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XANTHOMATOSIS AND THE RETICULO-ENDOTHELIAL SYSTEM

CORRELATION OF AN UNIDENTIFIED GROUP OF CASES DESCRIBED AS DEFECTS IN MEMBRANOUS BONES, EXOPHTHALMOS AND DIABETES INSIPIDUS (CHRISTIAN'S SYNDROME) *

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DETROIT

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INTRODUCTION

Xanthoma was first described as a rare disease of the skin. It is still classed as a dermatologic condition, although for a long time it has, in all its many forms, been considered a systemic process with lesions of the skin and tendon sheath as outward manifestations. Its common characteristics are, macroscopically, the sulphur yellow to

* From the Children's Clinic.

yellow brown color of the lesions, and microscopically, the presence of large bright cells with vacuolated or "foamy" protoplasm, in consequence of a high content of a fatlike substance.

In the early study, xanthoma was occasionally regarded as an inflammatory process of toxic or infectious origin, though it was more often considered neoplastic in nature. The discovery that the fatlike substance in the cells is lipoids, by Panzer, in 1906, and by Pinkus and Pick, in 1908, modified these views. Since then, xanthoma has come to be considered as a variable symptom complex resulting from a disturbance of lipoid metabolism, especially of cholesterol metabolism, and related to different causes.

With the work on the reticulo-endothelial system, a new interest has been brought into the xanthoma problem. The researches on this subject indicate that all the varied manifestations of xanthoma can be brought back to the single pathologic principle that certain substances infiltrate the reticulo-endothelial system. The xanthoma cell is a cell of reticulo-endothelial origin infiltrated with lipoids. Xanthoma lesions are the hyperplastic reaction of the reticulo-endothelial system, resulting from the infiltration of lipoids in excess in the body fluids. A localization of this process produces the hyperplastic nodular lesions.

According to this interpretation, xanthoma represents the body's attempt to rid the body fluids of lipoid which cannot be properly excreted and which acts as an irritant. Various lipoids (cholesterol fatty acid esters, phosphatid lipoids, possibly more complex lipoproteins) are concerned in this process, but the anisotropic ester of cholesterol has been most often observed and most studied.

This new view, though supported by animal experimentation, lacks clinical confirmation. I have had the good fortune to see two cases illustrating this condition; one case was studied at necropsy and one patient is still under clinical observation. Recent interest in reticulo-endothelial investigation makes the presentation of these cases opportune. They represent a form of xanthoma of a so-called visceral type, xanthomatosis Chalatow, in which many parts of the reticulo-endothelial system show storage of lipoid or hyperplasia of lipoid cells. In their consideration I shall discuss a group of cases already described by Christian and others under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus," in which the etiology is in doubt and which, I believe, represent the same condition.

The study of this series of cases in which hyperplasia of the lipoid cells occurs both as a diffuse process in various organs and as localized nodular lesions clears up in a surprising way the mystery of the destruction of bone, exophthalmos, diabetes insipidus and dwarfism in the syndrome and explains the pathogenesis of a number of other well recognized clinical conditions. It also contributes a new interest to the much

discussed relationship of other reticulo-endothelial lipoid metabolic conditions, notably Niemann's disease and Gaucher's disease. Xanthoma of this form is usually regarded as a rare condition, and as my cases contain so many features of clinical, as well as microscopic interest, I record them in full.

REPORT OF CASES

CASE 1.—*History*—H. S., a white boy, aged 5 years and 2 months, was referred to me on Dec. 14, 1925. The father was living and well. The mother was overweight, had congenital nystagmus and was neurotic; she had not had any miscarriages. One other child, a girl, aged 2 years, was well developed and healthy. The mother's pregnancy had been normal. The birth was not difficult and had occurred at full

Fig. 1 (case 1).—Extreme exophthalmos persisting post mortem.

term. At birth the infant was well developed and weighed 8 pounds (3,628.74 Gm.). He had been breast fed for fifteen months. The first teeth erupted at 6 months. At the age of 10 months, the infant weighed 26 pounds (11,799 Gm.). He had a mild facial eczema and a small abscess on the scalp at 11 months, otitis media at 12 months, and nasal diphtheria at the age of 1½ years, although it was not severe and he received antitoxin.

At the age of 2 years, following a mild attack of measles, the patient did not appear as well as usual. Six months later his tonsils and adenoids were removed. A soft swollen area was found on the back of his head at this time, which, it was thought, might have been due to a fall down some steps. As he did not complain of pain, a physician was not consulted until the child was 3 years and 9 months of age, when another swelling and soft spot appeared in the right temporal region; the mother ascribed this to his striking his head

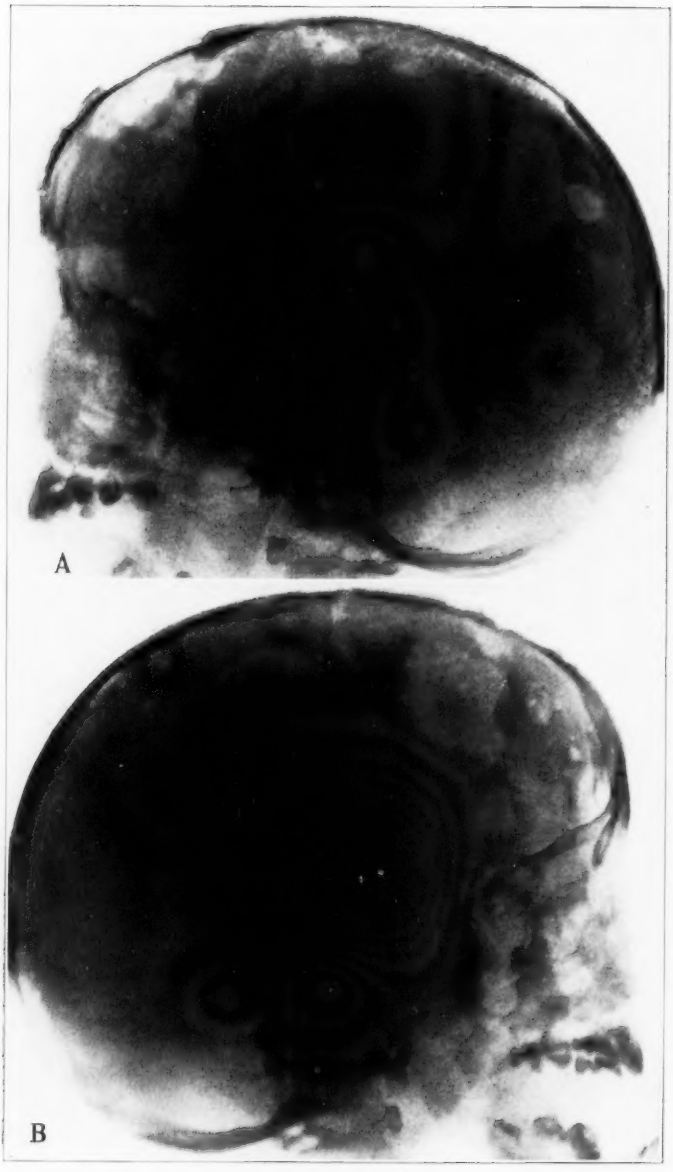

Fig. 2 (case 1).—Lateral aspects of extensive bone defects at the vertex and base of skull and at the maxillae, Dec. 15, 1925; *A*, right side; *B*, left side.

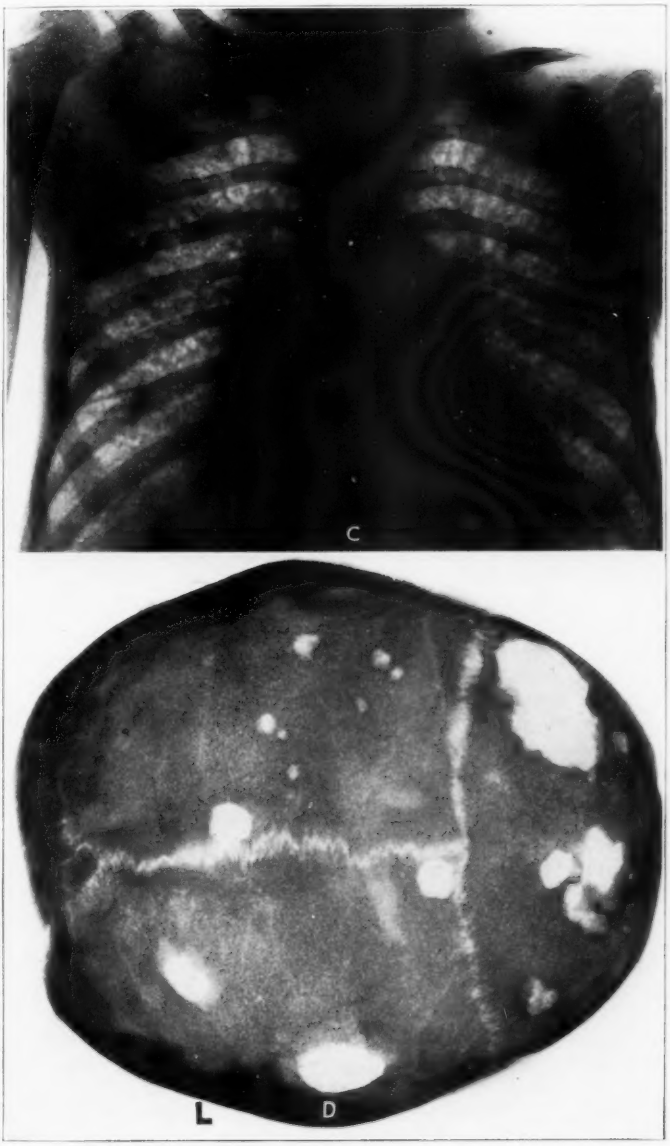

Fig. 2 (case 1).—*C* shows extreme pulmonary fibrosis on Dec. 15, 1925; *D*, appearance at autopsy, Jan. 3, 1926, showing the character of the borders of the bone defects; some of them are sharp and discrete in outline, whereas others have a more or less motheaten appearance.

against the corner of a table. Examination at this time showed a marked degree of exophthalmos and strabismus. The vision and eyegrounds were normal. The alveolar processes were swollen and tender, and most of the teeth were loose and infected, producing a foul odor to the breath. He had already lost a number of teeth, ten having been extracted at one time. There was a slight serous discharge from both ears, with questionable mastoid tenderness.

Roentgen-ray examination showed "multiple cranial defects involving both tables of the skull and one large defect in the occipital region of the skull where erosion of both tables was complete, suggesting a metastatic process, probably from sarcoma." The blood gave a negative Wassermann reaction. The Wassermann reaction of the spinal fluid was negative. The globulin was not increased. The colloidal gold curve was 0000000000. Neurologic symptoms were not found.

A mild pertussis developed, which made observation in a hospital impossible. The eyes, in the meantime, became more prominent, the right always more than the left, and the soft areas on the head gradually increased in size. The child did not complain of pain or headache, nor were tremor, irritability, convulsions or abnormal gait observed. His mother considered him bright, though his speech was not distinct, and it was believed that his hearing and vision were normal. His appetite and digestion were good. Abnormal urinary symptoms were not observed. He rarely wet his bed and did not show evidence of thirst or pass an unusual amount of urine. He was brought for examination because of the increasing shortness of breath and difficulty in walking, which had developed during the past three months. He had an occasional pain in the right side of the chest and a moderate dry cough and difficulty in breathing.

Physical Examination.—The boy was considerably undersize for his age; he was fairly well nourished, did not show abnormal deposits of fat and was pale, cyanotic and dyspneic. He weighed 29 pounds (13.2 Kg.) and was 38 inches (96 cm.) tall. The temperature was 100.2 F. The respiratory rate was 32. The skin was not especially dry and did not show any eruptions. The glands in the posterior cervical region were the size of shot; other glands were not enlarged. The head was large in proportion to the body; its circumference was 50 cm. The face was oval. There was a normal amount of brown hair. A noticeable bulge was present in the frontal region, in an area 5 by 7 cm., in which there was an absence of bone. This area protruded when there was straining, as in coughing and crying, and pulsation could be felt. Most of the bony edge was sharply defined. There was a similar area in the right temporal region, 4.5 by 3.5 cm., and a smaller area in the left parietal region, irregularly outlined, 2 cm. in diameter. At other points the surface was slightly elevated, as in the frontal region.

The eyes showed marked exophthalmos, greater in the right. The eye turned downward and inward. The pupils were slightly dilated, regular and equal, and reacted to light and in accommodation. The muscle response was normal and nystagmus was not present. The fundi appeared normal; the disks were well defined, and the vessels were normal in size and appearance.

There was a thin purulent discharge from both ears, more from the right. Both tympanic membranes were partially destroyed. The bridge of the nose had a sunken appearance, probably due to a bulge in the frontal region. The nasal passages were small due to evident swelling of the mucous membrane. The breath was foul. The alveolar arches were irregular and swollen and bled easily. Only three teeth remained; they were the lower incisors and were loose and covered with tartar-like substance. Tenderness and swelling were present over the maxillae, which added to the fulness of the lower portion of the face. The tongue was heavily coated a light brown. The throat was congested and a dull red,

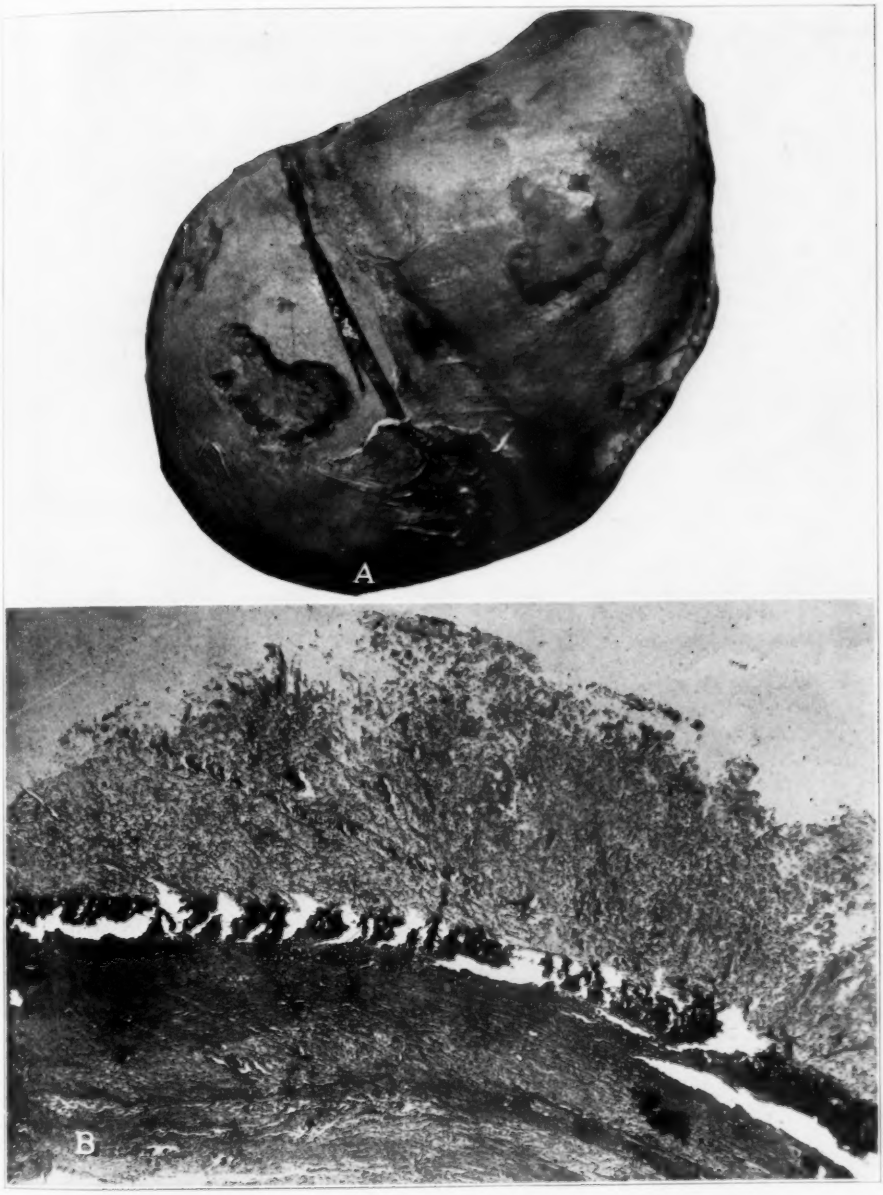

Fig. 3 (case 1).—*A* shows erosions of the calvarium, and *B* is a lower power photomicrograph of the hyperplastic dural plaque.

with thick purulent mucus dropping from the posterior pharynx. There was no evidence of tonsillar tissue. The thyroid was not palpable.

The heart showed a maximum impulse in the fifth space 1 cm. outside the nipple line. Cardiac dullness was heard 1 cm. to the right of the sternal border. The sounds were clear and distinct. Murmurs were not heard. The pulse was small and easily compressible, with a rate of 126. The blood pressure was: systolic, 80; diastolic, 40. The lungs were slightly hyperresonant throughout. The breath sounds were loud and distinct, without prolongation of expiration. Occasional coarse râles were heard in both bases. The abdomen was moderately distended but not tender. The spleen was not felt, and the area was not increased to percussion. The edge of the liver was felt 3 cm. below the costal margin in the mammary line. The genitals were well developed and normal. The spine showed slight prominence of the last dorsal vertebra. The muscles of the extremities were small and flabby. The hands and feet were normal in size and proportion. Clubbing of the finger tips was not present. There was slight edema of the lower extremities.

The knee reflexes were not exaggerated and were equal. The Babinski, Kernig or Brudinski signs were not elicited. The plantar reflexes were normal.

Routine laboratory examinations showed the following: The urine was straw colored, cloudy and alkaline, with a specific gravity of 1.012; albumin, sugar and acetone were absent. The sediment showed a heavy deposit of phosphates. The Bence-Jones albumose test was negative. Examination of the blood showed: hemoglobin (Dare), 57 per cent; red blood cells, 4,150,000; white blood cells, 17,350. The differential count showed: polymorphonuclears, 64 per cent; large mononuclears, 32 per cent; small lymphocytes, 4 per cent. The intradermal tuberculin test was negative. The blood Wassermann reaction was negative.

Roentgen-ray Examination (Dr. L. Reynolds).—On Dec. 15, 1925, examination showed multiple cranial defects of both tables of the skull. "The process involves especially the frontal and parietal, as well as the occipital bones, with the greater destruction taking place in the frontal bone. The maxillae are also involved and, to a lesser extent, the mandibles. The sella turcica is distinctly visible, there being some demineralization of the dorsum sella, but the pituitary fossa is of normal depth. The chest examination is very interesting as it reveals a diffuse bilateral fibrosis, the fibrosis simulating to a marked extent the pneumonoconiosis seen in mine workers' chests. The heart is definitely enlarged, both the right and left sides participating."

Clinical Diagnosis.—The condition was diagnosed as membranous defects of the bones; exophthalmos and dwarfism. Generalized xanthoma of a so-called visceral type was found.

Course.—Dec. 23, 1925: The patient had grown progressively weaker. He complained occasionally of pain in the right side. His cough was more distressing. Cyanosis and dyspnea were extreme. He was unable to sleep except when propped up in bed. He had no appetite and refused even fluids. He was almost continuously nauseated, and had vomited several times. The heart action was rapid, with a rate of 148. The pulse was small and easily compressible. No apex impulse was felt; the sounds were faint. The blood pressure was 70 systolic and 30 diastolic. Edema of the dependent parts of the body had increased. The boy was not thirsty, and passed little urine.

Laboratory Examination.—At this time, the urine was clear and alkaline, with a specific gravity of 1.012. Albumin, sugar, acetone and diacetic acid were absent. Microscopic examination gave negative results, except for an excess of phosphates.

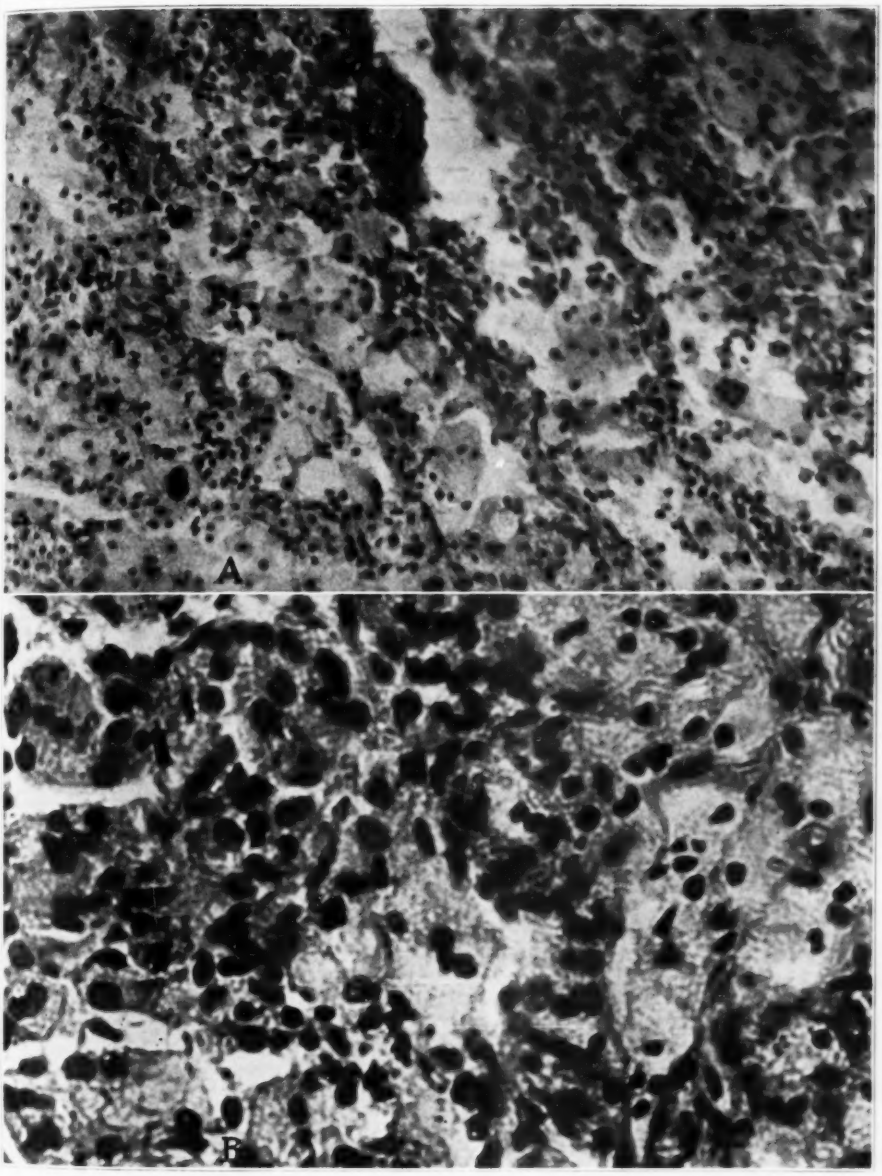

Fig. 4 (case 1).—*A* shows lipoid (foam) cells and foreign body giant cells in dural plaques; low power; *B*, lipoid (foam) cells and foreign body giant cells in dural plaque; higher magnification.

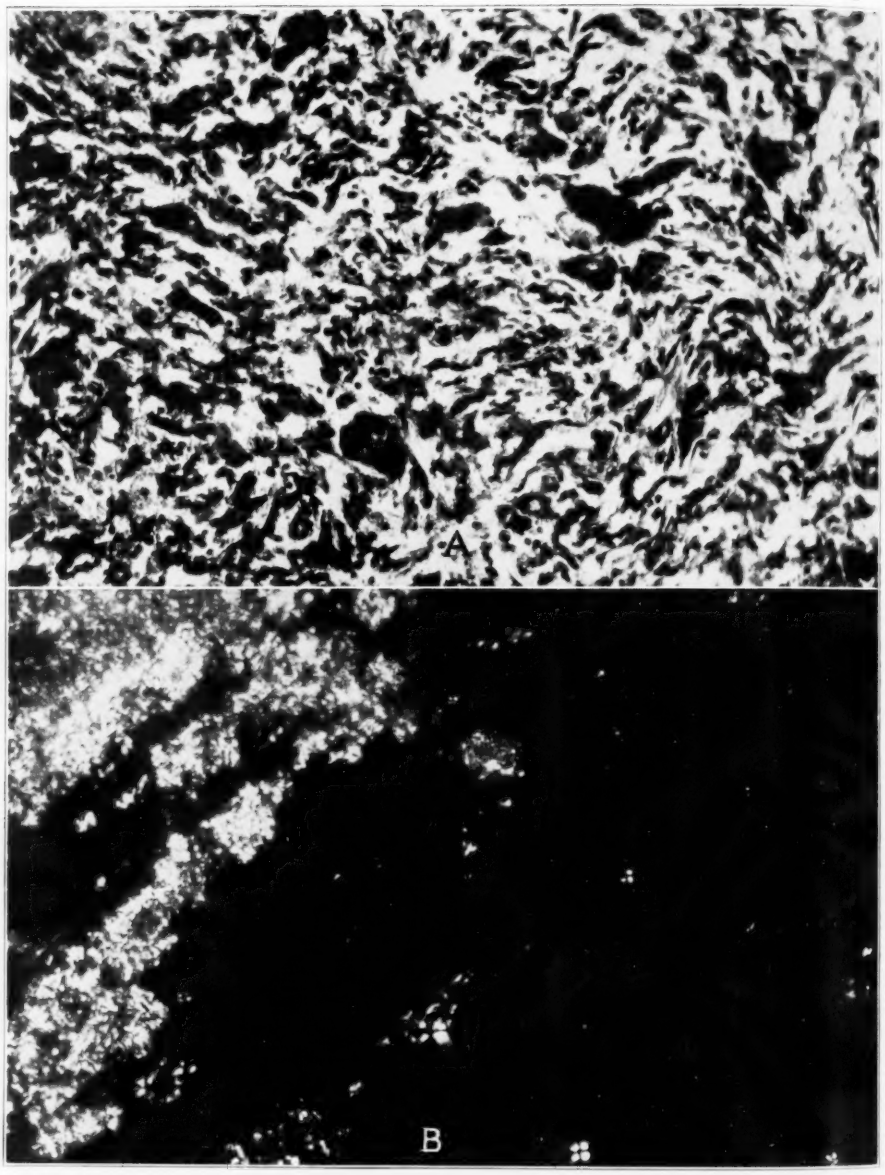

Fig. 5 (case 1).—*A*, dural plaque stained with sudan III, showing large amount of fat; *B*, section of dural plaque showing anisotropic fat as it appears in the polarizing microscope.

The blood showed: hemoglobin (Sahli), 64 per cent; red blood cells, 4,560,000, and white blood cells, 17,600. The differential count showed: polymorphonuclears, 73 per cent; large mononuclears, 20 per cent, and small lymphocytes, 7 per cent.

The patient was removed to Harper Hospital, Jan. 1, 1926, where he failed rapidly and died the following morning. The fatal termination was attributed to cardiac failure due to impaired circulation resulting from the extensive pulmonary fibrosis.

Autopsy Report (Dr. P. F. Morse, Jan. 3, 1926).—There was extreme pallor of the skin and marked exophthalmos of the type seen in cavernous sinus thrombosis. The fingers, toes and lips were markedly cyanosed. There was a serous discharge from both ears. Palpation of the skull revealed many cranial defects in which the bone appeared to be missing.

When the head was opened, the scalp was found normal in appearance. When the calvarium was exposed, there were numerous annular defects of the cranial bones which varied in size from 0.75 to 4 or 5 cm. in diameter. These defects had slightly wavy edges, but were fairly sharp. The bone at the margin was firmer than normal and the defect itself was filled with a gummy, semicaseous bright yellow tissue of rubbery consistency. The tissue appeared to be uniform in structure and on section presented the same appearance that it did externally. When the skull cap was removed, it was found that the tissue was easily pushed out of these defects, leaving a somewhat ragged hole in the skull. This tissue appeared to arise from and be continuous with the dura and to give the impression of a peculiar form of granulomatous tissue arising from the dura and invading the skull. The brain was somewhat edematous. The dura stripped easily from its superior surface. When the brain was removed, a gross lesion of the brain substance or ventricular system was not discovered. When the base of the skull was inspected, it was found irregularly covered over with these yellowish, granulomatous swellings which had destroyed a large portion of the bone of the base, extending forward into both orbits and completely surrounding the region of the hypophysis and destroying the sella turcica. The nasal sinuses showed nothing of note. When the temporal bone was opened, the tympanic membranes were found destroyed, and there was a marked atrophic inflammatory process of both middle ears without destruction of the bone.

When the body cavities were opened in the usual manner, the sternum appeared normal with a normal marrow content. The heart was markedly enlarged and dilated, both right and left. When the heart was removed, there was a moderate hypertrophy of the muscle of both ventricles and relative dilatation of the tricuspid and mitral rings, but no other cardiac lesion. The first portion of the aorta and coronary vessels appeared normal. The lungs were voluminous and felt fibrous to palpation. The left lung was somewhat adherent over the posterior lateral aspect of the costal pleura, the adhesions being of the same peculiar yellowish, gummy nature that was noted in the granulomas of the skull. When the lungs were removed, they were found distended and firm to the touch and on section presented a remarkable appearance. The whole lung was a mass of communicating vesicular cavities. These cavities varied in size from that of a pin head to that of a large pea. The septums between the cavities were fibrous and inelastic. The walls of the blood vessels were somewhat thickened. The general appearance suggested a low grade pulmonary hypoplasia, or an intense or diffuse form of pneumonitis with marked emphysema.

When the abdomen was inspected, the liver was found to be about normal in size. When it was sectioned, it did not present a remarkable appearance. The spleen was normal. Both kidneys were normal in size and on section presented a

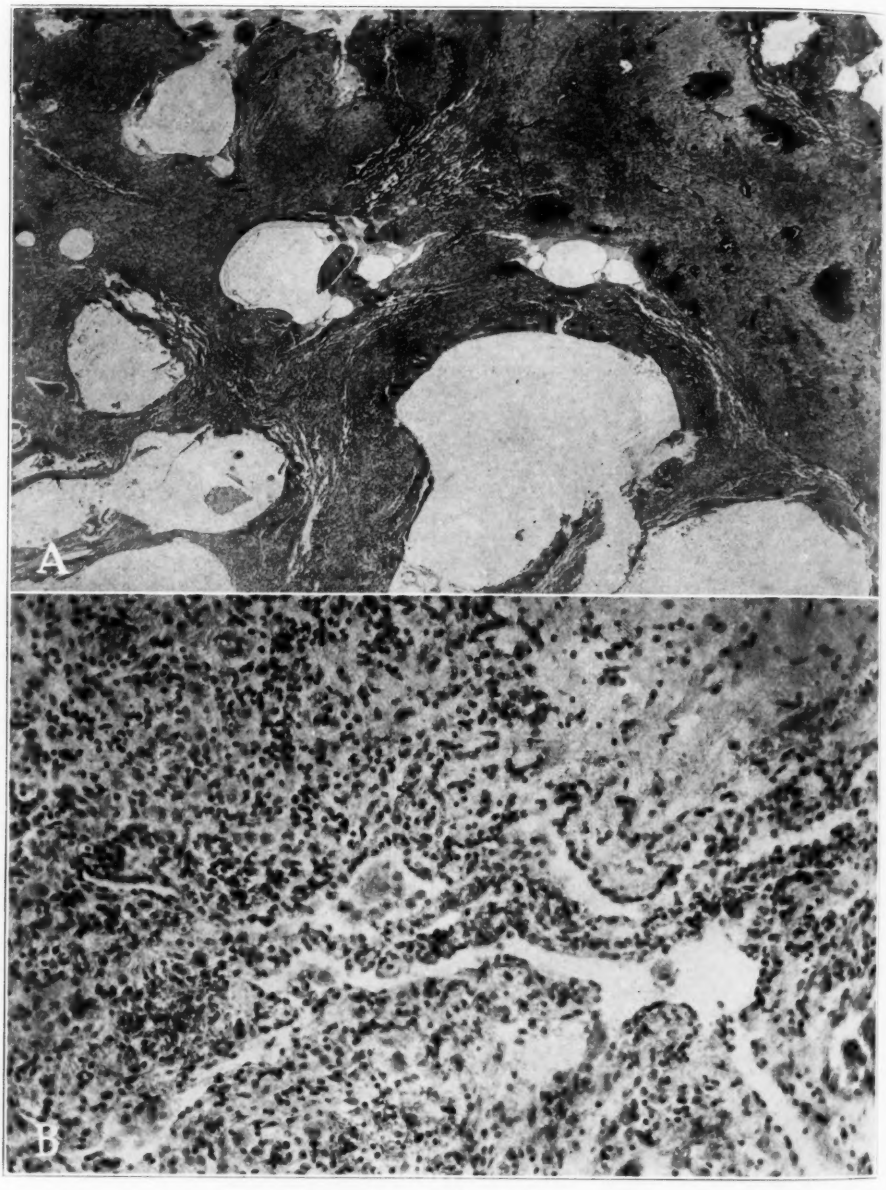

Fig. 6 (case 1).—*A* shows chronic bronchopneumonia with patches of fibrosis and alternating patches of emphysema; *B*, chronic bronchopneumonia with localized patches of fibrosis.

normal relation of the cortex to the medulla. The capsule stripped easily. The gastro-intestinal tract, including the pancreas, did not present gross pathologic changes. The pelvic organs were normal. When the ilia were exposed there was found in the cavity of the right ilium a yellowish plaque about 1 cm. in diameter with a bone defect of the same character as that seen in the skull. A similar yellow plaque 2 cm. in diameter protruded from the periosteum on the right side of the body of the first lumbar vertebra.

"Roentgen-ray study made of the skull cap at the time of the autopsy reveals in a striking way the cranial defects that were observed in the x-ray study of the skull during life: some of the defects show a very sharp discrete outline of their

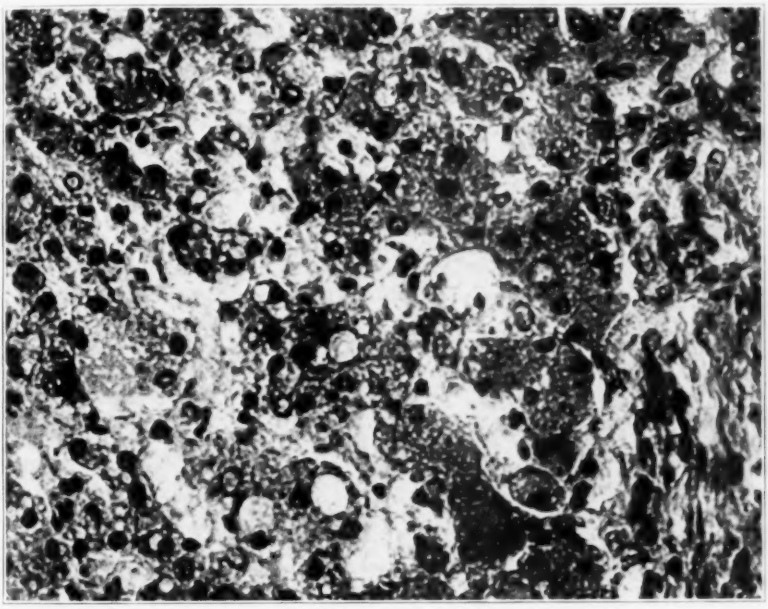

Fig. 7 (case 1).—Photomicrographic appearance of liver showing slight lipoidosis of the liver cells with marked lipoidosis of the Kupffer cells.

'bony borders,' whereas others have a more or less moth eaten appearance. This is especially true of the frontal bone on the right side." (Dr. L. Reynolds.)

Pathologic Report (Dr. A. S. Warthin).—The thyroid gland showed a colloid content normal for this age, with undeveloped adenomatous tissue. Throughout the gland, there were a number of sharply circumscribed areas of proliferation of the stroma having an epithelial appearance in the center with some lipoidosis.

The suprarenals showed hypoplasia which was especially marked in the medulla. Moderate lipoidosis of the cortical cells was present. In the perisuprarenal tissue there were small areas of proliferating reticulo-endothelium. The large epithelioid cells showed more lipoidosis and some pigmentation, thus resembling xanthoma cells. In one section in the medulla were small areas of proliferating reticulo-endothelial cells with lymphocytic infiltration.

The lymph nodes showed lymphoid exhaustion of the germ centers. Proliferation of the reticulo-endothelium with lipoidosis and slight pigmentation was present. The proliferation of the reticulo-endothelium and lipoidosis varied greatly in the different nodes, being quite marked in some, while others showed them to a slight degree. All through the retroperitoneal tissue there were bands and strands of this atypical tissue.

The kidneys were congested with edema and some lipoidosis of the renal epithelium. Small concretions of lime salt were found in some of the tubules. Proliferation of the reticulo-endothelium and lipoidosis were not found.

Sections from the brain did not show any pathologic change except slight edema.

The liver presented marked passive congestion. There was slight lipoidosis of the liver cells, more marked in the periphery of the lobules, and some atrophy of the cells. Many lipoid Kupffer cells were found.

Chronic bronchopneumonia, with localized patches of fibrosis and alternating patches of emphysema, was found in the lungs. The reticulo-endothelial cells around the pulmonary vessels showed the same hyperplasia and lipoidosis seen elsewhere, and projecting into the larger bronchi were papillary overgrowths of fibroblastic tissue and reticulo-endothelial tissue showing lipoidosis. The pleura was thickened with reticulo-endothelial hyperplasia and lipoidosis.

The muscle fibers of the heart were fairly well developed for this age. Little lipoidosis of the muscle and no reticulo-endothelial proliferation and no lipoidosis in the stroma were found. The testes were apparently normal for the age. Lipoid cells were not found in the testes or epididymis.

The pineal gland was edematous and congested. Lime salt deposits or lipoid cells were not present.

The bones showed atypical marrow. There was reticulo-endothelial hyperplasia with many multinuclear giant cells and many lipoid cells. Rarefaction of the bony trabeculae was found. (The bone absorption resembled that seen in some cases of osteomalacia.)

The dural plaques consisted of masses of lipoid-containing cells of reticulo-endothelial type resembling xanthoma. Throughout were numerous multinuclear giant cells. In old tissue of the dura were numerous small calcareous concretions. In lipoid masses were areas of cholesterol crystal formation, with cholesterol clefts and with many multinuclear giant cells. Giant cells, evidently foreign body giant cells, surrounded the cholesterol crystals. These plaques did not suggest infectious granuloma but resembled xanthoma or masses of cells of the xanthoma type, and probably consisted of proliferated reticulo-endothelial cells with cholesterolosis. Fat stain showed cells to be loaded with lipoids.

Case 2.—*History.*—R. R., a white boy, aged 3 years and 11 months, was referred for further study from the clinic of the Children's Hospital of Michigan, Feb. 14, 1926.

The parents were living and well. They had three other children, aged 11, 9 and 7 years, respectively. The oldest, a boy, had rheumatism and chronic cardiac disease. The maternal grandmother was operated on for cancer of the breast when she was 50. The maternal grandfather suffered from kidney stone. The paternal great grandfather died with diabetes mellitus. The family history did not show evidence of tuberculosis, syphilis, asthma or renal disease. There was no further history of cardiac disease, diabetes or malignant disease.

Both the pregnancy and the birth had been normal. The patient had been a "fine strong baby," weighing 8¾ pounds (3,968.94 Gm.). He had been breast fed for four weeks, and then was given a mixture of cow's milk, milk sugar and lime

water. He did not receive cereals or cod liver oil, but was given orange juice from the age of 3 months on, and vegetables and broth during the latter part of the first year. After the first three months, he developed rapidly, had teeth at 6 months, stood with support at 8 months and walked at 14 months. He did not catch cold easily or have sore throat. There were no illnesses during the first year. He had a moderately severe attack of pertussis when he was 1½ years old.

When he was a little under 2 years, he became irritable, complained of a sore mouth, began to ask for water frequently and to pass large amounts of urine.

Fig. 8 (case 2).—Left exophthalmos; normal proportions of body.

His mother ascribed these symptoms to teething. When 22 months old, he was standing in a rocking chair and tipped over sidewise, striking his head. For three or four days following this, he was drowsy, irritable, complained of pain and slept a good deal. The soreness of the mouth grew worse, and several of the teeth loosened and came out. At 26 months, he had a second fall, after which considerable swelling appeared over the frontal bone. This was again followed by drowsiness and some stupor. About this time he had suppurative otitis media on the left side. The symptoms of thirst and frequent urination were variable. His mother stated that if he were allowed to drink at the tap he would some-

times fill himself until he complained of pain and finally vomited clear water. She estimated that he passed from 6 to 8 quarts (5,678 to 7,570 cc.) of urine daily and that he asked for a drink of water every hour. When 2 years and 6 months old, on Sept. 12, 1924, he was admitted to the Children's Hospital of Michigan. Examination showed a well nourished boy, who did not appear sick but who was irritable and fussy. In the left parietal region a cranial defect the size of a nickel was noted, also small palpable glands involving the posterior cervical chain. His abdomen was slightly distended. The rest of the physical examination gave negative results.

Laboratory and Special Examinations (from the Children's Hospital record).—The urine was clear and alkaline, with a specific gravity of from 1.030 to 1.003;

Fig. 9 (case 2).—Left exophthalmos.

albumin and sugar were not present. The Bence-Jones albumose test was negative on repeated examinations. Microscopic examination gave negative results. Examination of the blood showed: red blood cells, 3,850,000; white blood cells, 9,800. The differential count showed: polymorphonuclears, 71 per cent; large mononuclears, 3 per cent; small lymphocytes, 26 per cent. The urea nitrogen was 16 mg. per hundred cubic centimeters. The blood sugar was 60 mg. per hundred cubic centimeters. The blood Wassermann reaction was negative. Two dextrose tolerance tests showed blood sugar well within normal limits. The amount of urine was not increased by the test, nor did the sugar appear in the urine. The response to pituitary was pronounced at first, but the dosage had to be increased and was discontinued before the patient left the hospital, because the therapeutic effect was not satisfactory. The Pirquet test was negative. The

cerebrospinal fluid was clear and came under normal pressure. The cell count was 8 per centimeter; the globulin and the spinal fluid Wassermann tests were negative.

X-ray Examination.—A report on Sept. 16, 1924, stated: "The skull shows evidence of multiple cranial defects. One large defect involves the entire base of the skull and fronto-temporal region on the right side. The process has entirely destroyed the floor of the sella, only the anterior clinoid processes and dorsum sella remain as landmarks. A large defect also appears in the left parietal region near the vertex of the skull with a smaller one in the vertex. There is evidence of involvement of the fifth rib on the right side in the posterior axillary region. No involvement of the long bones, but an area of decreased density in the right ilium."

During the patient's stay of more than two months in the hospital, his temperature ranged from 97.6 to 99.7 F., with an occasional unexplained elevation as high as 101. For about a week, there was moderate elevation of temperature, resulting from a small abscess in the right buttock which was opened and drained. A rise also occurred following resection of a portion of the fifth rib which, according to the x-ray reports, showed changes similar to those in the skull. A specimen was taken for microscopic examination, but a report was not made. The pulse rate varied from 110 to 140, and the respirations, from 24 to 30 a minute. The weight fluctuated considerably with variations in fluid intake and output, but it was 23 pounds and 7 ounces (10,631 Gm.) on admission and 21 pounds and 14 ounces (9,922 Gm.) on discharge.

The following possibilities were considered in the diagnosis at this time: "Luetic destructive process, sarcoma or myeloma. Patient discharged Nov. 20, 1924, unimproved, to return when the condition became more serious."

When I first saw him, on Feb. 14, 1926, fifteen months after he left the hospital, the patient had not had any acute illnesses. His appetite and digestion were good. He complained of only moderate thirst and passed from 6 to 8 quarts of urine in twenty-four hours. His mother had noticed that he had not grown like her other children. Besides polyuria and polydipsia, his chief complaint was sore mouth. His mother had not noticed the fact that the left eye protruded more than the right eye, but she said that the soft spot on the head had increased in size. There had not been any complaints of headache, digestive upset, visual disorder, diplopia, vertigo, fainting spells or convulsions. The mother thought that the hearing was acute and the mental state normal.

Physical Examination.—The boy appeared fairly well, and was not in pain or distress, though he was irritable and fussy. The nutrition and color were fairly good. The skeletal proportions were normal, though small for his age. He weighed 28 pounds (12,690.5 Gm.), and was 35 inches (88.9 cm.) tall. The temperature was 99; pulse rate, 116, and respirations, 26. The skin was clear, elastic and dry, without any eruptions. The panniculus was well developed, without abnormal deposits of fat. The glands were not enlarged. The head was symmetrical and square in type, with a normal amount of light brown hair. On palpation, an irregular oblong defect was felt in the skull in the left parietal region near the vertex, 3 by 4 cm. The edges were sharply defined. There was little, if any, tenderness on pressure. The left eye was slightly more prominent than the right. The pupils were equal and regular and reacted to light and in accommodation; the sclerae were blue; photophobia, diplopia, nystagmus, or palsies of the extrinsic eye muscles were not present. Von Graefe's sign was not present. The fundi appeared normal. The ears were normal. The nose was small; its

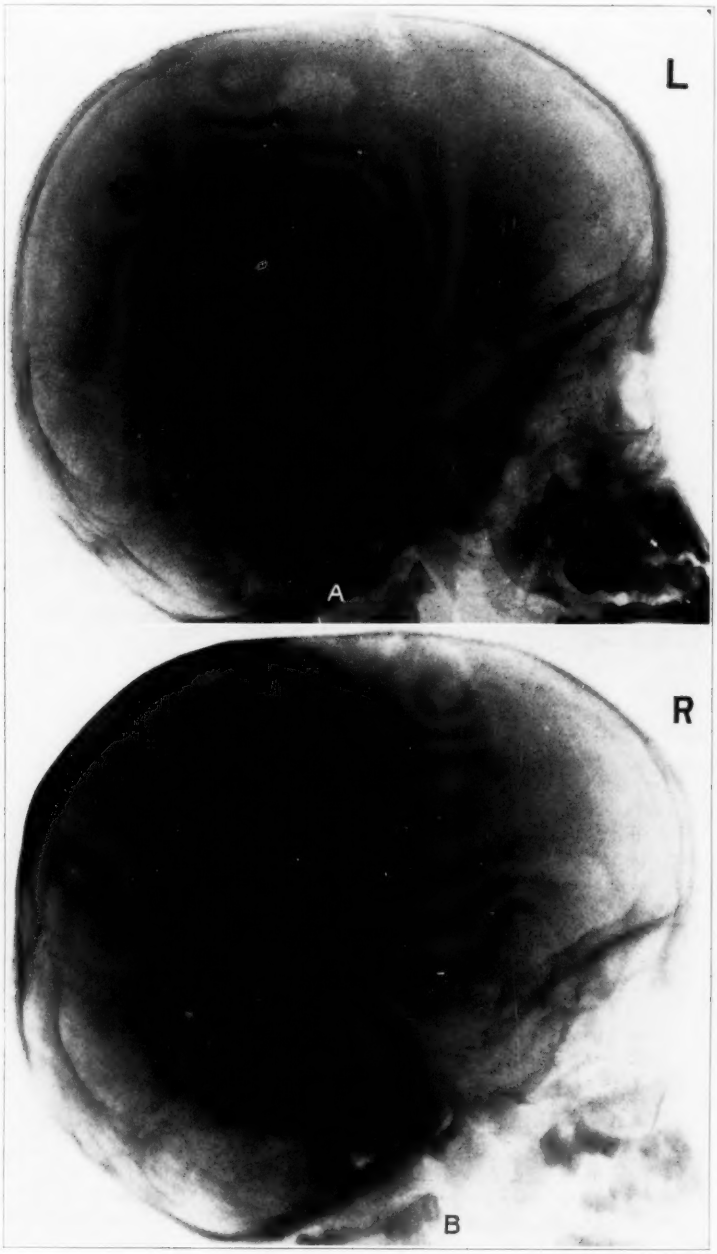

Fig. 10 (case 2).—*A* shows bone defect in parietal region and extensive defect at base of skull, Sept. 16, 1924; as compared with *A*, *B* shows a gradual increase in the bone destructive process at the vertex and base of skull and in the maxillae, Nov. 1, 1924.

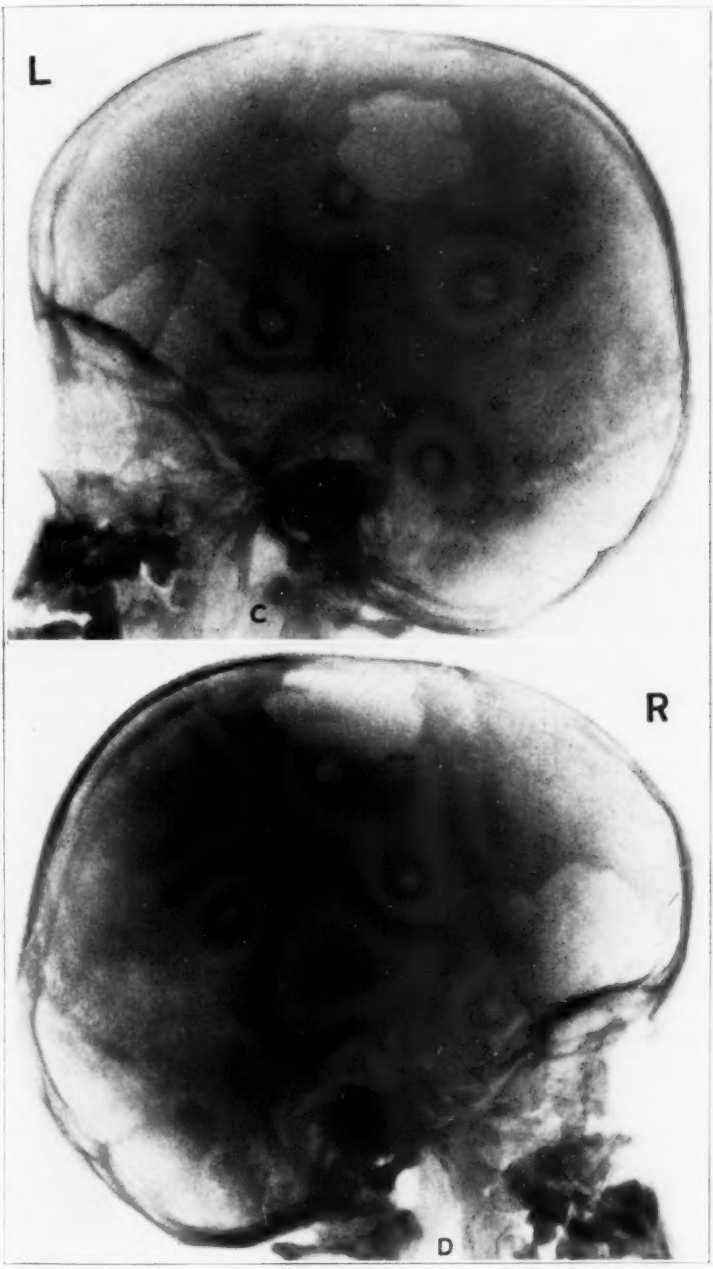

Fig. 10 (case 2).—On Feb. 20, 1926, the lateral aspects show that the bone defects at the vertex and base of skull are much more extensive than on examination seventeen months before; *C*, right side, and *D*, left.

Fig. 10 (case 2).—*E* shows, on Oct. 27, 1927, the remarkable regeneration of bone in the areas which showed progressive bone destruction twenty months before; *F* shows the remarkable degree of bone regeneration on Nov. 27, 1927, twenty months after examination in *D*.

passages were narrow; the mucous membranes were swollen, and there was a slight nasal discharge. The mouth was small; the gums were swollen and tender, bled easily and were retracted from the teeth. All the molar teeth in both the upper and the lower jaw were loose. The teeth appeared normal. Pus could be expressed about some of them. The tongue protruded in the median line without tremor. The tonsils were moderately enlarged and with the pharynx were congested. The voice was of good quality. The neck did not show abnormal pulsations. The thyroid was not palpable. The heart showed an apex impulse in the fifth space just inside the nipple line. The action was regular, the sounds of good quality, and no murmurs were present. The lungs showed good resonance, and normal breath sounds were heard throughout. The abdomen was moderately distended but not tender. The spleen was not felt. The edge of the liver was palpable below the costal margin in the nipple line. The superficial and deep reflexes of the extremities were all normal. The genitals were normally developed.

Roentgen-Ray Examination (Dr. L. Reynolds).—On Feb. 20, 1926, roentgen-ray examination revealed: "Marked extension of the bone erosion which has involved the right and left parietal bones. The process has extended posteriorly and now involves the temporal bones on both sides, continuing on the right side as far as the occipital bone in the region of the lateral sinus. There is definite involvement and destruction of the mastoid cells, excepting one or two cells seen in the region of the antra which are still pneumatic. In the film taken in the postero-anterior plane one is able to note the rather extensive process which has involved the supra-orbital plate on both sides, this process being more extensive on the right side, where there is very definite involvement of the frontal bone and extension into the superior and lateral orbital ridges. The maxillae are also involved. There is erosion of the lateral wall of the left maxilla and clouding of the antrum. The chest examination reveals evidence of repair of bony structure in the shaft of the fifth rib in the posterior axillary line, at the point where specimen was removed for biopsy. However, there has been an extension of the process anteriorly in the shaft of the fifth rib. None of the other ribs are seen to be involved and all the long bones are normal in appearance."

A determination of the blood serum cholesterol at this time gave a value of 315 mg. per hundred cubic centimeters (Myer-Wardell method).

Clinical Diagnosis.—The condition was diagnosed as membranous bone defects, exophthalmos, diabetes insipidus, and generalized xanthoma of a visceral type.

Laboratory Study and Special Examinations.—On April 18, 1926, the patient was admitted to Harper Hospital. In general these examinations corresponded to those previously made: The urine was amber, acid and negative for albumin and sugar, with a specific gravity of 1.000 to 1.004. It varied in daily amount from 5,000 to 6,000 cc. Under the administration of sodium chloride, there was little tendency to concentration, and the sodium chloride was readily excreted. The Mosenthal test demonstrated the large increase in excretion of water and that the amounts excreted during the day and night were in normal relation. The excretion of chloride and nitrogen was within normal limits. Solution of pituitary given by mouth had no effect, but obstetric pituitary solution given hypodermically reduced the amount of urine to normal and did not materially affect the specific gravity. The dextrose tolerance test showed: fasting, 0.087 per cent; one hour, 0.117 per cent; three hours, 0.083 per cent. The urine was not increased, and sugar did not appear in the urine. Examination of the blood showed: hemoglobin (Sahli), 68 per cent; erythrocytes, 5,600,000; leukocytes, 13,500. The differential count showed: polymorphonuclears, 67 per cent; large mononuclears, 7 per cent; small lymphocytes, 24 per cent, and eosinophils, 2 per cent. Six separate exami-

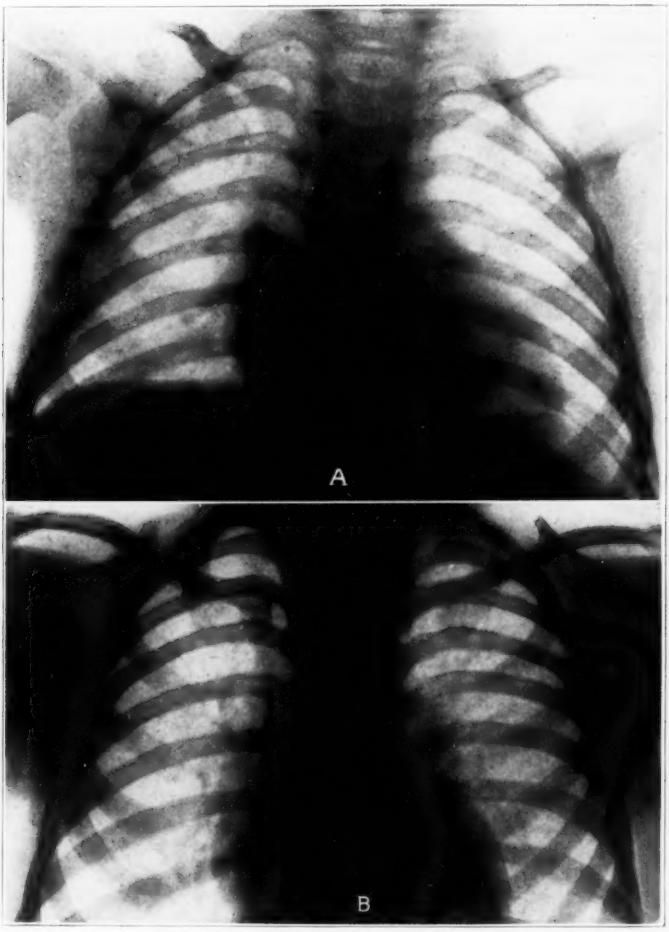

Fig. 11 (case 2).—*A* shows erosion in fifth rib on the right side, on Nov. 6, 1926; *B*, almost complete healing, on Nov. 27, 1927, of erosion in fifth rib on right side with formation of callus where specimen for biopsy was taken.

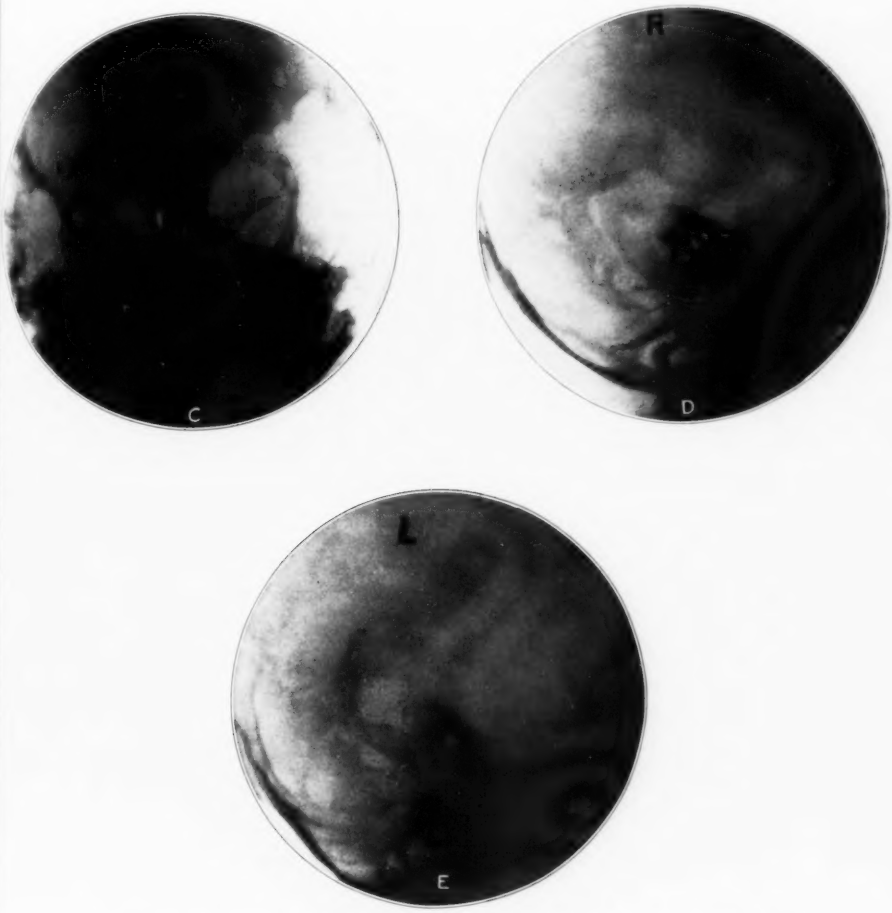

Fig. 11 (case 2).—*C* shows extensive bone destruction about the orbits, especially marked on the left side, on April 26; *D*, extensive destruction involving the right mastoid, on April 26; *E*, extensive bone destruction involving the left mastoid and base of skull, on April 26.

nations of blood cultures gave negative results; one showed contamination, and two anaerobic cultures were negative. Blood chemical determinations showed: nitrogen, 23 mg.; sugar, 60 mg.; calcium, 9 mg.; uric acid, 4 mg.; cholesterol, 256 mg.; fatty acids, 400 mg., all per hundred cubic centimeters of blood serum. The spinal fluid showed: cell count, 8; globulin, negative; colloidal gold, 000000000; Wassermann, negative; cultures from the fluid did not show growth, and injection into guinea-pigs gave negative results. Intradermal tuberculin tests were negative. Basal metabolism tests were attempted but were considered unsatisfactory. Pharmacologic tests, in which varying doses of anterior lobe pituitary and obstetric pituitary solution hypodermically were used, did not give an unusual reaction that could not be regarded as normal, suggesting that a disturbance of pituitary function had not occurred.

Growth Characteristics (Dr. C. J. Marinus).—On April 22, 1926, examination showed: "The face is definitely square in type, some flattening of the nose, small mouth, eyes slightly suggestive of mongol type. Skin definitely dry. Hands and feet good size and proportion. Measurements: Circumference of head around forehead, 19 inches; vertical across the jaws, 20 inches; largest circumference, 21 inches. Neck, 9½ inches; shoulders, 20½ inches; chest, 20 inches; abdomen, 19 inches. Span, 34½ inches; sitting height, 19½ inches; lower half, 16½ inches; upper arm, 9½ inches; lower arm, 10½ inches; thigh, 10½ inches; leg, 10 inches. These measurements are normal, the height being slightly greater than the span, and the lower half somewhat less than the upper half. There is no evidence of insufficiency of anterior lobe of pituitary as shown by bone development. There is no deficiency of posterior lobe as shown by lack of fat changes. The dryness of the skin is that usually seen in diabetes insipidus due to disturbed water balances rather than that due to thyroid insufficiency. At the present time this patient does not show any developmental changes characteristic of pituitary disease. There is a moderate dwarfism which is, however, not characteristic in type. The signs, by which I am accustomed to diagnose pituitary insufficiency, do not usually appear before the age of 8. This case is of particular interest, because the x-ray examination presents positive evidence of pituitary damage and because of the diabetes insipidus. The proportions, in anterior lobe deficiency, tend to resemble those of infancy, so that in a patient of this age it is impossible to say whether the decrease in height is due to pituitary insufficiency or falls in the class of true dwarfism."

Ophthalmologic Examination (Dr. Parker Heath).—On April 24, 1926, examination showed: "Vision in each eye, as determined by objects, is normal for distance and near. Convergent power normal; no paralysis of extrinsic muscles. Pupils equal in diameter and react promptly to light and in accommodation; consensual reflexes are present. The left eye is slightly more prominent than the right, being proptosed approximately 2 mm. There is none of the lid lag sign found in exophthalmic goiter. Neither globe is congested. Ophthalmoscopic examination of the right eye: pupil dilates evenly, media clear, disk normal in color, rings slightly blurred, vessels normal in caliber and course, foveal reflexes present. The left eye is essentially the same. The mechanism of the exophthalmos, judging from x-ray plates, may be due to letting go of the apex of the orbit, as suggested by a previous observer."

Roentgen-ray Report (Dr. L. Reynolds).—On Oct. 27, 1927, the report stated: "At this time there has been a striking change. The previously noted large cranial defects show complete bony degeneration, except for a very small discrete area in the left parietal bone, where a large defect was formally observed. One is able to make out only the faintest cranial defect and this is limited to the inner

table. The very large defects noted in the region of the anterior and middle fossa on the right and left sides show complete regeneration. There has been, however, no attempt at repair of the sella turcica, although the supra-orbital plates show distinct bony repair. The pelvis and long bones reveal no evidence of abnormality, and at no time has there been any destruction of the long bones, other than the shaft of the fifth rib on the right side."

Course.—On Nov. 8, 1927, the patient appeared well, was lively and had a good color. Measurements showed that he had gained 3½ inches (8.8 cm.) in height during the past year. The exophthalmos had noticeably receded. The soft spot in the left parietal region was markedly reduced in size, so that it could be located only with difficulty. The sinuses and teeth were in good condition. The boy rarely asked for water and passed less than 3 quarts (2,839 cc.) of urine during the day and about half this amount at night, in comparison with twice that much a year ago. A determination of cholesterol showed 111 mg. per hundred cubic centimeters of blood serum.

RÉSUMÉ OF CASES SHOWING CHRISTIAN'S SYNDROME

In 1919, H. A. Christian, under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus—an unusual Syndrome of Dyspituitarism," reported a case presenting this syndrome and cited two similar cases previously described by Schüller. Since then Hand has recorded three cases, including one of Kay's. Grosh and Stiffel, Thompson, Keegan and Dunn, Danzer, and Kyrklund have each reported one case.

The syndrome is so striking and the symptomatology so similar that there can be no doubt of their representing the same disease as that in the two cases I have just described.

Christian's patient, a girl, aged 5 years, was normal and healthy until 3 years of age. At this time her teeth became loose and her gums swollen and tender. She had never been ill, except that she had mumps three or four months previously. When she was 3½ years old she developed thirst and polyuria, and the right eye became prominent. Examination at 5 years showed defects in the bones of the skull, exophthalmos, loose teeth with swollen gums, some of the teeth missing, and typical diabetes insipidus. The Wassermann and tuberculin tests were negative. Neurologic symptoms were not present. Christian considered the condition as probably due to disturbed pituitary function.

Schüller's first patient, a boy aged 16 years, had a severe fall on the abdomen at the age of 6 years. Following this accident he suffered nocturia. His growth was retarded and he later developed the picture of dystrophia adiposogenitalis. When he was 12 years old, a discharge began from his left ear. Exophthalmos was first observed at the age of 15 years. Examination showed extensive cranial defects. On both sides of the neck above the clavicle were "fatty tumors." Schüller ascribed the condition to a tumor at the base of the brain, an angioma of either the dura or skull bone.

Schüller's second patient, a girl of 4 years, was normal up to the age of 1½ years, when she had whooping cough. When 2 years old she developed thirst and polyuria, and exophthalmos was first noted. She was under observation for a number of years, during which time there was some retrogression in the defects of the skull. The diagnosis was "anomaly of the skeleton resulting from disease of the hypophysis."

Hand's first patient was a boy, aged 3 years, who complained of thirst and polyuria, which had begun eight weeks previously. He had enterocolitis at 5 months and measles and croup at 2 years. The child was undersized and poorly

nourished, with light brown hair and bronzed dry skin. The skin of the abdomen was covered with petechiae and "an eruption something like scabies." Later these spots increased in number and were elevated, appearing over the body and extremities. His eyes were in a condition of exophthalmos, giving him a "frog-like" appearance. Polyuria and polydipsia were pronounced. At autopsy, when the scalp was removed, a yellow nodule the size of a five cent piece was noticed near the right parietal eminence. When the skull cap was removed, this nodule was seen on the inner side, evidently arising from the dura, besides other similar areas eroding the skull. The lymphatic glands in the mesentery, mediastinum and all through the body were enlarged. Bronchopneumonia of both lungs, caseous pleuritis of the right lung and warty endocarditis of the mitral valve were found. In the pelvis of each kidney was a hard yellow mass. The diagnosis at the time was tuberculosis, but Hand stated that he doubted the diagnosis himself.

Hand's second case, originally reported by Kay under the title "Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria," was in a boy, aged 7 years, who was healthy up to 4 years, at which time he had scarlet fever followed by a persistently discharging right ear. Four months after he had had scarlet fever, he had swollen cervical glands. When he was 4½ years old, the "gums began to separate from the teeth." This was followed by gradual loss of his teeth, beginning with the molars. At the same time soft spots appeared on the head where there seemed not to be any bone. When he was about 5 years old, exophthalmos was observed and shortly afterward polyuria and thirst suddenly developed. He passed 27 quarts of urine daily. He was much undersized for his age. It was observed that his breathing was stertorous. The bones were normal except for extensive cranial defects and similar changes in the maxillae. Kay evidently thought that the condition was due to a tumor at the base of the brain.

Hand's third case was in a boy, aged 4 years, who had had a tumor-like swelling removed from the left parietal region at the age of 2 years. There had been an absence of bone at this point, and the mass appeared to have arisen from the dura. The pathologic report of the tissue removed was "No gumma, no sarcoma, slight degree of inflammation, mainly a myxomatous change." Since then other swellings had appeared and exophthalmos, greater on the left side, had developed. In this report Hand stated that "no polyuria has developed as yet." The x-ray showed marked cranial defects, but "no involvement of the sella turcica," and "so no symptoms of diabetes insipidus."

Grosh and Stiffel's patient, a girl, aged 7 years, was weak and did not develop from the second year. She was markedly underweight and underheight. At 6 years she began having trouble with her teeth and with the left mastoid, which was opened and drained. Her mouth became sore with a bullous eruption on the gums, which necessitated the removal of some of the unerupted permanent teeth. Seven weeks after the operation on the mastoid she suddenly developed polyuria and thirst. Examination showed a bad condition of the teeth and gums, extensive cranial defects, dwarfism, typical diabetes insipidus and unilateral exophthalmos. There were similar bony defects of the maxillae and left ilium. When she was observed three years later, there was hardly any increase in her size, no obesity and the genitals were normal. The left ear was still discharging. The cranial defects had increased slightly. There was no x-ray evidence of involvement of the sella turcica.

Thompson, Keegan and Dunn's patient was a pale, poorly nourished boy of 9 years. At the age of 7½ years, he had a severe attack of measles. Following this, he was in a weakened condition and the gums became sore and the teeth

loosened. Six months after the measles, excessive thirst and polyuria suddenly developed, persisted for only a few days and then disappeared. At this time, soft spots on the right side of the head were observed. A year after he had had measles, polyuria and thirst again appeared. The boy was emaciated, with a sallow skin. There was moderate exophthalmos, marked gingivitis and clean and sound but loose teeth. The x-ray showed extensive bony defects of the skull, described as "geographical skull." The sella turcica appeared normal, but there were extensive similar defects in the maxillae, pelvic bones, upper portion of the right femur and ribs. The body of the fourth lumbar vertebra was collapsed. A tentative diagnosis of multiple myeloma was made. This patient was under observation about eighteen months, during which time he grew progressively worse. He became pale and emaciated, suffered from backache and pain in the left hip and walked with a marked limp, listing forward to the left. Exophthalmos was marked. The entire skull was soft and doughy, with only an irregular framework of supporting bony ridges. The gingivitis was severe, and the teeth were held by soft investing tissue as the alveolar processes had been absorbed. The x-ray of the chest revealed a diffuse increase in density, characteristic of chronic interstitial pulmonitis. As death approached, the cough and dyspnea became more troublesome. The end came suddenly, and was attributed to impaired circulation incident to intense pulmonary fibrosis. At autopsy, the scalp showed fibrous adhesions. The inner surface of the dura was mottled by dull yellowish white tissue, which took sharlach R fat stain. The large yellow infundibulum stalk was fibrosed. There was involvement of the petrous portion of the mastoid and the middle ear. The ethmoid cells were obliterated by the same tissue growth. The pathologic diagnosis in this case was "exophthalmos; decalcification of bones; fibrosis of the tuber cinereum; slight subacute inflammation of the pars posterior of the pituitary gland; chronic interstitial fibrosis of the lungs; hypertrophy of the heart; chronic passive congestion of the liver and spleen; hypertrophy of the kidneys and bladder." From their histologic study, Thompson, Keegan and Dunn considered the condition "inflammatory, rather than degenerative or a primary metabolic (endocrinologic) process."

Danzer's patient was a boy, aged 4½ years, who had recently had his tonsils removed. He was miserable, having had repeated attacks of sore throat. Two months after the operation, his mother first noticed soft tender spots on his head. He was pale and stoop-shouldered, with exophthalmos, bad teeth, spongy gums and many soft spots on his head. He complained of thirst and polyuria, which had evidently developed suddenly a year after the soft spots were first observed. The x-ray showed extensive cranial defects and similar changes in the maxillae. Danzer made no comment regarding the bones of the rest of the body and did not discuss the etiology.

Kyrklund's patient, a girl, aged 12 years, was normal up to the age of 2 years, at which time she developed a cough, began breathing rapidly and became emaciated. At 4 years she developed thirst and polyuria. At the age of 7, she suddenly became fat, walked stiffly and complained of pain in the legs. The skin of the head was so tender that she could not stand having her hair combed. Growth was noticeably retarded, as was mental development. She was dyspneic. Her lips, hands and feet were cyanotic. She had the typical appearance of dystrophia adiposogenitalis. Examination showed that there were numerous cranial defects. The long bones were normal. The teeth were in bad condition and exophthalmos was present. At autopsy, the scalp was adherent to the calvarium around the soft areas and when separated, yellow detritus-like material flowed out leaving cystlike depressions. The inner table in these places was

eroded and the space filled with brownish yellow tissue arising from the dura. The dura had grown firmly to the inner table and showed yellowish brown, tumor-like thickenings. The region of the hypophysis did not show macroscopic changes, but there were growths in the brain stem behind the hypophysis of the same brownish yellow color. There were extensive changes in both lungs and pleura. "The structure of the lesions, on the whole, was similarly formed of connective tissue cells, part round cells, and some spindle cells. Lesions in the brain stem contained irregularly formed giant cells. The histological process did not simulate tuberculosis." Kyrklund considered the "condition due to a tumor of sarcomatous nature," and believed the "diabetes insipidus secondary to the growth in the region of the hypophysis."

CHRISTIAN'S SYNDROME AND XANTHOMATOSIS

I first associated this series of cases with xanthoma on purely clinical grounds. In 1922, Griffith reported "A Case of Xanthoma Tuberosum, with Early Jaundice and with Diabetes Insipidus." His patient showed defects of the membranous bones, exophthalmos and diabetes insipidus, as well as cutaneous lesions of xanthoma. Later this patient came to autopsy, and was studied carefully by Wiedman and Freeman.

Xanthoma, supposedly a rare disease, has been the subject of a surprising amount of study. While this adds a great deal to the better understanding of the varied problems of xanthoma, the many researches lack the clinical evidence, which this unique group of cases, "Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus," might contribute.

HISTORICAL CONSIDERATION OF XANTHOMA IN RELATION TO CHRISTIAN'S SYNDROME

As there is little discussion of xanthoma in works on general medicine and so much of interest in the dermatologic and special pathologic literature, a consideration of the investigations which have led up to the present interpretation of this process is important. A study of the anatomic and microscopic features will establish the identity of this unique syndrome, as well as contribute to a better understanding of the pathogenesis.

GENERAL ACCOUNT OF THE CLINICAL PICTURE

Constitution.—Several clinical forms of this condition, characterized by yellow to yellowish brown lesions containing special large cells, have been observed and described in the dermatologic literature, the one most frequently noted being the familiar orange yellow plaques or nodules on the eyelids: xanthoma or xanthelasma palpebrarum. This variety occurs most often in adults past middle age. Less often, and especially in young children, a generalized eruptive form, xanthoma multiplex, is seen. Associated with the cutaneous manifestations are

tendinous, peritendinous and periarticular lesions: xantho-myeloma of the tendon sheaths. At times a special generalized eruptive form appears in glycosuric subjects: xanthoma diabeticorum. In a few instances, as a result of studies made at autopsy, nodules and plaques involving certain internal structures are observed: generalized visceral xanthoma or xanthomatosis. The lesions in this type may appear on the various mucous membranes; there may be involvement of the cardiovascular system, especially the inner walls of the larger vessels and heart valves, or of the serous surfaces, the periosteum, pleura, pericardium, capsule of Glisson, dura and peritoneum. Finally, there are instances in which, as a result of histologic study, the mesenchymal portion (reticulum and endothelium) of certain organs—the liver, lymph nodes, spleen, bone marrow, suprarenals, hypophysis, thymus, pancreas and lungs—are found to be affected by the process. This form occurs at all ages and is frequently associated with icterus, glycosuria or diseases of the kidney in adults. In young children in whom icterus and glycosuria are rare complications, these cases are often congenital or there is a family history. This type is observed sometimes with, often without, skin manifestations.

General Comment.—Xanthoma was first described by Rayer, in 1836, under the French title—"Plaques jaunatres des paupieres." Sixteen years later, Addison and Gull published their monograph "Vitiligoidea." In 1863, Erasmus Wilson proposed the name xanthelasma, meaning yellow plaques; and W. F. Smith, in 1869, because of the tumor-like appearance of the yellow nodules, gave the name now generally used, xanthoma.

The early study was, for the most part, clinical, and was concerned with the separation of the different forms, the consideration of symptomatology and the report of interesting cases. Addison and Gull first described the multiplex variety, studied the relationship to diseases of the liver, and observed a case associated with glycosuria. Balzer described the tumor-like forms arising from tendinous, peritendinous and periarticular surfaces. The works of Pye-Smith, Murchison, Fagge, Crocker, Chambard and others made known the mucous membrane and visceral localizations as they occur in adults. To these varieties Hutchinson, Sangster and Crocker, a committee appointed by the London Pathological Society in 1882, added juvenile xanthoma, separated because of its occurrence before puberty.

Crocker published a good clinical report of the early dermatologic literature, and recently G. Levy reviewed the entire subject. Weber and Stewart presented suggestive clinical discussions; Wustmann, a consideration of the histopathogenesis of the nodular lesions; Aschoff, Kammer, Kawamura, Chalatow and Versè have made important contributions. In our own literature, Beeson and Albrecht have reviewed the multiplex

variety, and Knowles and Fisher, this form as it occurs in early childhood. McWhorter and Weeks have considered the tumor-like forms arising from tendon sheaths from the surgical point of view. Major has reviewed the cases associated with glycosuria, and recently Oppenheimer and Fishberg have discussed a case of this type in its relation to the reticulo-endothelial system. Their patient was a girl, aged 6 years, who had extensive visceral involvement.

Symptomologic Considerations.—Many cases of unusual clinical interest with lesions not confined to the skin were recorded in the early literature. Von Graefe and Virchow observed yellow plaques on the mucous membranes of the cornea and conjunctiva. A patient of Pusey and Johnstone had corneal involvement. Crocker observed yellowish-white patches on the tongue of an infant, aged 3 months. Dyer and also Fordyce saw patients with involvement of the lips and buccal mucous membranes. Posner's patient had lesions of the gums and palatine arch. In Hardaway's patient, besides involvement of the penis, scrotum and the area underneath the nails, the xanthomatous eruption was distributed like herpes zoster over the ninth and tenth ribs. Kreibeck recently described a similar zosteriform xanthoma associated with lesions of the mucous membranes and skin. Pusey and Johnstone's patient also had nodules in the larynx. Murchison recorded a case in which lesions of the skin were associated with nodules the size of peas about the hilum of the liver and splenic capsule, both these organs being enlarged as well as the lymph nodes and the spleen. There were also yellow patches on the heart valves and yellow areas in the posterior wall of the stomach. In addition to an extensive eruption of the skin, Pye-Smith observed xanthoma-like areas on the mucous membranes, peritoneum and about the hilum of the liver and splenic capsule, "associated with jaundice." As early as 1872, however, he noted that it was not real jaundice and remarked that "the lesions about the gall-bladder looked like atheroma of the arteries."

Clinical and Symptomologic Considerations Concerning Syndrome.—There are a number of cases recorded in the literature that are of interest in connection with the syndrome I have described. Notable among these is a somewhat similar group occurring in adults, with extensive involvement of the serous surfaces, reported by Proescher and Meredith, Dietrich, and Nöthen.

Dietrich's patient had exophthalmos and was thought to have had some pulmonary disease. He died of cardiac failure. The autopsy revealed what Dietrich called fibroxanthosarcoma. There were retroperitoneal masses extending along the spine from the abdominal to the thoracic cavity. Yellow nodules, the size of kernels of corn, were thickly scattered over the surface of the liver, splenic capsule, the pleura and pericardium. Larger yellow masses were found in both orbits and

surrounding the vessels at the base of the brain. The hypophysis was pushed out of the sella turcica by the "tumor masses."

Yellow, tumor-like, xanthoma nodules involving the dura and sometimes associated with exophthalmos have also been mentioned by Pinkus and Pick, Kirch and Weber and Schmidt.

There is no mention of diabetes insipidus in Proescher and Meredith's, Dietrich's, or Nöthen's cases, but such cases have been recorded by Crocker, Futcher, Spillmann and Watrin, Pusey and Johnstone, Turner, Davidson and White and Griffiths. Probably the patients of Weber and Schmidt, Siemens and Fahr and Stamm had this complication.

Crocker's patient had diabetes insipidus and "gouty tendencies." Futcher's patient was an adult and had xanthomatous changes involving the hilum of the liver, with jaundice as well as diabetes insipidus. Besides extensive lesions of the skin the case of Turner, Davidson and White showed involvement of the tongue, epiglottis, trachea, bronchi, lungs, mucous membranes of the stomach, mediastinum and pituitary region. This patient also had diabetes insipidus with yellow xanthoma nodules surrounding the hypophysis. Pusey and Johnstone's patient, a boy, aged 17, besides extensive xanthoma lesions, showed a marked degree of dwarfism as well as diabetes insipidus. Spillmann and Watrin's patient, a girl, aged 9 years, with generalized papular xanthoma, was undersize for her age. She had thirst and polyuria.

Both Pusey and Johnstone's and Spillmann and Watrin's cases showed features similar to those of "Christian's syndrome," but Griffith's case, already referred to as representing "defects in membranous bones, exophthalmos and diabetes insipidus," was the most striking.

Griffith's patient, a much undersized boy of 9 years, had been healthy and normal up to 2 years. At the age of 2½ years, he had pertussis. At 3 years he had a temporary enlargement of the abdomen and "yellowness." Growth was evidently retarded from this time. At 8 years he had another attack of jaundice and swellings on the head following contusion, and an eruption appeared all over the body. The child was undernourished and underdeveloped, with extensive cutaneous xanthoma eruption, evident exophthalmos, marked irregularities of the teeth, defects in the skull and typical diabetes insipidus. Autopsy revealed yellow masses about the hilum of the liver and arising from the dura. The hypophysis was displaced by the xanthoma mass.

Berkheiser reported a case under the title "Multiple Myeloma of Children," which obviously also belongs in the group I am describing.

Berkheiser's patient was a girl, aged 3½ years. She had had a normal first year, except for a mild attack of measles at 9 months. Exophthalmos was first observed when she was 16 months old. She complained of pain in the right leg, hip and arm, and difficulty in walk-

ing. She was irritable and gave a history of bed wetting. The x-ray revealed extensive bony defects of the cranium, the pelvis, the upper portion of the right femur and the lower portion of the left humerus. Interest in this patient was directed to the orthopedic condition. There was no mention of the urinary symptoms, but a study was made of one of the lesions which will be considered later.

Other cases are recorded in the literature, most often occurring in young children but sometimes in adults, that could be brought into relationship with this unique syndrome purely on clinical grounds. The juvenile type I have described unites the entire group in a striking manner. This is shown more fully in the histologic study.

PATHOLOGIC CONSIDERATIONS

Microscopic Changes.—In the early literature, the histologic studies of the lesions were associated with the clinical observations. Most interest centered about the character of special cells. Waldeyer, Virchow, Kaposi, deVincentiis, Chambard and Touton described the morphology of these cells. According to Chambard, the xanthelasmic cells are variable in size and form, with an abundance of protoplasm and small darkly staining nuclei. In the fresh state, the protoplasm is loaded with small fatty droplets. Treated with ordinary fixing reagents, which dissolve out the fat, the protoplasm becomes a fine areolar network giving a foamy or vacuolated appearance; hence, the name "foam cell" or "Schaumzelle."

These cells never show karyokinesis. They are found free in the layers of connective tissue, frequently surrounding the blood vessels, or are grouped in islets separated by fibers of connective tissue. Sometimes they are fused to form a multinuclear mass with nuclei disposed as a corona or demicorona giving the aspect of giant cells. Associated with these cells, there is a variable connective tissue reaction and sometimes round-cell infiltration. Occasionally typical foreign body giant cells with nonfoamy protoplasm and more scattered nuclei occur in relation to fatty crystals.

This structure appears as a diffuse process, or is grouped to form the xanthoma plaques and nodules. Early in its development the xanthoma cells, with increased vascularity, are in excess, while in the older nodular lesions the connective tissue growth predominates, appearing greatest in the larger and firmer lesions.

The fatty substance exists, generally, either as fine granules or as round droplets, but sometimes as crystals in small rods or fine needles, united in clusters. It is for the most part contained in the cells, although occasionally it is found in the intercellular spaces.

These fatty granules usually present themselves under two aspects: (*a*) those which stain poorly with osmic acid, taking a brown color, stain

orange with sudan III, and show double refraction with polarized light, i.e., cholesterol fatty acid esters; (*b*) those which stain deep black with osmic acid, turn red with sudan III, and remain dark when the prisms of the polariscope are crossed, i.e., neutral fats or glycerine fatty acid esters (Darier).

These two granular forms are found to exist together, but are irregularly and diversely distributed, and at times there are remains of red blood cells and iron pigments in these lipoid-containing cells (indicating phagocytic properties). They owe their appearance to the substances which infiltrate them and, in swelling, separate the cytoplasm. The perivascular distribution, variable connective tissue reaction, sometimes round-cell infiltration and the presence of fatty and pigment granules and giant cells produce the varied appearance of the lesions. It is these special lipoid-containing cells which particularly characterize the varied xanthoma manifestations.

Microscopic and Clinical Changes.—Chambard, Touton and Török observed xanthoma cells in the diverse skin lesions. Dor observed the same cells in the nodular forms arising from tendinous, peritendinous and periarticular surfaces. Chvostek first found foam cells in yellow nodules about the hilum of the liver. Coats early observed foam cells in the spleen of diabetic persons with lipemia. Particular attention was not given to these cells in the inner organs, until Schultze reported in 1912 "Concerning Large Cell Hyperplasia in a Case of Diabetes with Lipemia." Since then an entire new series of cases has been brought into relationship with the clinical forms already described. Some of these cases show and some do not show skin manifestations. Aschoff, Kawamura, Marchand and Chalatow made important observations in this regard.

In Schultze's case, the entire splenic pulp was replaced by foam cells, and other organs were not involved. Lutz reported two similar cases, one showing atheroma in the aorta and the other, changes in the lungs. Schultze and Lutz considered this condition related to Gaucher's disease.

Marchand found lipoid-containing cells in the spleen and lymph nodes and was the first to observe this change in the bone marrow. Williams and Dresbach found lipoid-containing cells in the spleen, liver, lymph nodes and suprarenals. In M. Smith's patient they were mostly confined to the spleen, but to a small extent appeared in the liver and lymph nodes. Oppenheimer and Fishberg's patient, previously mentioned, showed much more extensive changes. There were lipoid-containing cells in the spleen, liver, endothelium of the aorta, adventitia of the cutaneous vessels, and also changes in the kidneys and mitral valve. These changes all occurred in patients with diabetes mellitus associated with lipemia.

There is still another group of cases that may be brought into relation with xanthoma. In 1914, Niemann described a condition in an infant which he regarded as histologically different from Gaucher's disease, but which was similar to the large cell hyperplasia reported by Schultze. Siegmund described a similar change in an infant, aged 9 months. He observed lipoid-containing cells at the hilum of the liver and spleen. The Kupffer cells of the liver, the reticulo-endothelial cells of the spleen, the bone marrow, heart valves, glomeruli of the kidney, and excretory tubules also were involved. Knox, Wahl and Schmeisser and Bloom have reported similar cases.

The lipoid-containing cells in this group of infants are the most extensive in distribution. According to Bloom, they are observed in the spleen, thymus, mucosa of the intestines, free in the alveoli of the lungs and in the walls of the blood vessels of the lungs, kidneys, pancreas and in the Kupffer cells of the liver; M. Smith added that they were also found in the bone marrow and brain tissue in one case. In this group there is considerable phosphatid lipoid but also some double refractive lipoid. In the literature this series has usually been referred to under the title of Niemann's disease, and has been regarded as different from Gaucher's disease (Mandelbaum, Bloom and Oberling).

A case reported by Fahr and Stamm has generally been included with the series just described, but I wish to show that it also closely resembles, clinically and histologically, the group I am discussing, Christian's syndrome.

Fahr and Stamm's patient was a weak, undernourished, underdeveloped girl, weighing 18 pounds (8,164.6 Gm.) at 3 years. Fahr thought that she had some disturbance of carbohydrate and protein metabolism. He also questioned whether there might not be a hyopophyseal disturbance. She had always had thirst and had not grown. Her skin was dry, and the hair, which had turned a lighter color, was falling. She died in uremic convulsions. At autopsy the lipoid-containing cells were most noticeable in the lymph nodes of the "lymphatic portal ring," less in the spleen, and least in the Kupffer cells of the liver.

In my first case there were lipoid-containing cells in the lymph nodes, Kupffer cells of the liver, suprarenals, few in the kidneys and thymus and many in the lungs and the nodular lesions of the dura, peritoneum and pleura; in Griffith's patient, examined by Weidman and Freeman, there were extensive xanthomatous changes of the skin, lymph nodes, liver, bile ducts, lungs, pineal gland, infundibulum, pituitary and dura. Possibly the glia cells were involved.

Microscopic Changes Concerning the Syndrome.—Weidman and Freeman stated "that the organs in their patient reflected only the general sclerosing effect which makes many of the tissues resemble, under

the microscope, those of a subject dying of senility." This is why most of the cases in the series here presented, which have come to autopsy, have not been identified with xanthoma. In their histologic studies of xanthoma skin nodules, Pollitzer and Wile demonstrated that the early lesions are made up almost entirely of foam cells; lesions a little more advanced show foam cells and spindle cells with considerable connective tissue reaction, and finally, some of the older lesions are composed almost entirely of spindle cells and fibrous tissue.

In the case that Thompson, Keegan and Dunn described, there was such an advanced process that in many places only spindle cells, secondary reactions and fibrosing effects were observed. Their patient showed extensive xanthomatous changes about the hypophysis, base of the brain, dura and lungs, similar to the changes in my first case, only in a later stage of development. The condition of the little girl described by Berkheiser represents a less advanced stage and, as he says, was regarded by Maximow as xanthomatous in character. In Kyrklund's case, the underlying process was not recognized for the same reason, but I believe that it represents the same pathologic change with the variations which are characteristic of this condition.

In this group, another case reported by Schultz, Wermbter and Puhl under the title "A Granuloma-like System Disease of the Hematopoietic Apparatus: Hyperplasia of the Reticulo-Endothelial System" should be included. Their patient, a girl, aged 2½ years, had extensive defects of the bones and dwarfism. The histologic study showed that the process was quite advanced. The nodular lesions arising from the dura had all changed to fibrous tissue. The lesions in the orbit and at the base of the brain looked like thickened tendon. The yellow nodules and diffuse changes in the lungs resembled those found in the lungs in my first case. There was more extensive involvement of the organs, especially the bone marrow and spleen, and more tendency to a nodular type of lesion in the organs, than in any of the cases I have previously described. Schultz, Wermbter and Puhl considered the condition a disease of the reticulo-endothelial system and supposed an infection of unknown type to be responsible.

Study of Microscopic Changes; Conclusions.—The study of the microscopic changes, besides bringing into relation with xanthoma several forms not previously recognized as such, determines certain other facts regarding the chemistry and character of the lesions:

1. Xanthoma represents a mixed steatosis in which, although double refractive cholesterin esters are most often observed, phosphatid lipoids and other more complex lipoids (lipoproteins in Gaucher's disease) are also concerned, and these lipoids are always in association with glycerin fatty acid esters.

2. The lesions are extremely variable in their histologic appearance. At first they are made up largely of foam cells and later, almost entirely of spindle cells and connective tissue. In the early stage the lesions may be vascular, while in a later stage the vascular supply is limited. In the older lesions there are frequently no lipoid-containing cells, only special forms of fibrous tissue, and cellular reactions and secondary changes occur which mask the picture generally.

3. The process is an extensive one, not simply confined to the skin and certain internal structures, such as the mucous membranes, the walls of the large vessels, heart valves and serous surfaces, but it may also involve the mesenchymal portion of the blood and lymph vessels generally.

Finally, the study shows that this condition occurs at all ages, usually appearing as discrete nodular lesions in the slowly evolving adult forms and as a more diffuse process in the rapidly developing infantile cases.

The significance of these observations will be more fully discussed in the consideration of the pathogenesis.

PATHOGENESIS IN RELATION TO HYPERLIPOIDEMIA AND THE RETICULO-ENDOTHELIAL SYSTEM

Pathogenic Theories.—Many opinions have arisen as to the nature of the varied xanthoma manifestations. Addison and Gull regarded xanthoma as a local disease. Hutchinson, observing the frequency of jaundice, thought that diseases of the liver and gall passages were of etiologic importance. Hilton Fagge and Pye-Smith, finding visceral lesions, regarded xanthoma as a systemic process and referred icterus and glycosuria back to the visceral localizations.

Most of the early studies disregarded these clinical symptoms in favor of various cellular theories. Potain considered the cutaneous lesions enlarged skin glands. Unna and Balzer, observing giant cells, were inclined to believe in an infectious origin. Chambard and Renaud proposed that the xanthoma cells might be connective tissue cells, analogous to macrophages loaded with fat. Chambard and Török, observing round cells, especially in the diabetic form, considered the lesions of inflammatory nature. The most frequent interpretation, however, was neoplastic. For Virchow, xanthoma was a neoplasm of the connective tissue with fatty deposits or fatty degeneration of cells, and Touton, Koebner and de Vincentiis held similar opinions but regarded the cells as of endothelial origin. Török considered xanthoma as a neoplasm of the connective tissue resulting from the proliferation of cells arrested in an embryonic state. Crocker also regarded xanthoma as a neoplasm of the connective tissue. He considered the inflammation primary and the connective tissue growth secondary and the whole process of toxic origin.

Potain and Quinquard early proposed a humeral theory in relation to the hepatic dysfunction. Panzer, in Stoerk's laboratory, first indentified double refractive lipoids in the fat filled cells. Pinkus and Pick, finding double refractive lipoids in the various xanthoma lesions, declared hypercholesterinemia the probable cause of xanthoma. In a second research, in which they examined all the different xanthoma pictures, they concluded that an infiltration of connective tissue elements, reticulum and endothelium takes place. They believe that the nodules were neoplasms of the connective tissue, but wished to designate the change by the term "xanthomatosum," as a condition that might affect any new growth. In discussing his extensive case, previously mentioned, Dietrich objected to Pinkus and Pick's use of an adjective to designate this condition. He thought that there was a small group of xanthofibromas.

Hypercholesterolemia.—The actual demonstration of hypercholesterolemia was due to Chauffard and Laroche. They found hypercholesterolemia in several patients with xanthoma, as well as in an icteric patient afflicted with xanthoma. Chauffard and Laroche stated: "Special as this process is (the formation of cholesterin deposits), it is not, however, without an analogy in pathology and nothing could be more truthfully compared to it than the change which we find in another great humeral illness, gout. There also, a specific cutaneous deposition, the tophus, discloses an excess of uric acid circulating and then fixed. Each of these two toxemias makes itself concrete, as it were, in its own place of election, but the process is identical and the end is an aseptic and specific infiltration, so that one can conclude that xanthoma is to hypercholesterinemia as tophus is to an excess of uric acid contained in the blood serum of the gouty patient."

Hyperlipoidemia; Clinical Consideration.—Hyperlipoidemia, especially hypercholesterinemia, is now generally regarded as the most common fundamental cause of xanthoma. Since the original observations of Chauffard and Laroche in 1910, this has been repeatedly verified—by Schmidt; Arning and Lippmann; Burns; Levy, for the multiplex varieties; Major, Mook and Weiss, for xanthoma diabeticorum; Weil and Kirch, for the tumor-like forms arising from tendon sheaths; Spillmann and Watrin, and Griffiths, for the juvenile type I have described. Harrison and Whitfield reviewed this subject in 1923.

The cholesterol value in Griffith's patient was 397 mg. per hundred cubic centimeters of blood serum; in the similar case of Spillmann and Watrin, there were 595 mg. per hundred cubic centimeters of blood serum. In my first case, examinations were not made for cholesterol, but dural plaques examined in this regard showed high cholesterol content. In my second case, repeated determinations of cholesterol

were made. They varied from 315 mg. per hundred cubic centimeters of blood serum, in October, 1926; 256 mg. (250 mg., digitonin method), in April, 1927, to 111 mg. (Myers and Wardell method) in October, 1927.

The analysis of the clinical observations in relation to hypercholesterolemia is of interest. In the investigations of Schmidt and Levy, in which entire families were examined, it was found that hypercholesterolemia manifests itself in a different manner, according to the individual; it produced biliary lithiasis in one, atheroma in another, and brought on ocular symptoms in a third. It is only in certain subjects that it produces either xanthoma palpebrarum, or the cutaneous cholesterin infiltrations which result in the multiplex variety, or in extremely rare cases, in the tendinous, peritendinous and periarticular and visceral forms (Levy).

These investigations also determined that cholesterolemia, though considerable, does not always result in xanthoma eruption. This suggests the possibility of certain accessory factors, such as trauma and friction, or infection. Clinical observation permits the recognition of such accessory factors. Various authors have verified the fact that the skin eruption localizes, by preference, in places exposed to repeated trauma or friction, such as the elbows, knees, buttocks, shoulders and palms. Darier believed that he was able to attribute palpebral localization to frequent folding and rubbing of the eyelids. Chauffard and Laroche observed the eruptions appearing at the point of injections of sodium cacodylate in a patient with icterus. Major found it following mosquito bites. In a case described by Nicol, cutaneous xanthoma occurred after a quinine exanthem. In the cases of Hardaway and Kreibeck, the lesions were distributed like those in herpes zoster. Such an eruption probably accounted for the localization. The raised and thickened vaccination scars often observed sometimes result from the same cause.

In several of the group described trauma may have antedated the lesions on the head, but the process is too extensive for all of the lesions to be accounted for in this manner. In generalized visceral xanthoma in an adult diabetic patient, Lubarsch considered that for the lesions to develop, it was necessary for cholesterol to show stasis and accumulate for a long time, mainly in the lungs. This might have happened in the cases here described. As shown by the studies made at autopsy, there has invariably been a marked degree of pulmonary fibrosis and xanthomatous change in the lungs. In case 1, the fibrosis was so advanced that it gave the impression of being the primary lesion.

In this connection the secondary importance of infection is apparent. Weber wrote that "it is highly probable that a person may have a

hypercholesterolemia for years without developing xanthoma lesions, but some influenza-like infection may give rise to inflammatory changes and be followed by lipoid deposits." There was no evidence of syphilis or tuberculosis in the group of cases I have described, but several authors have suggested the possibility of these infections playing such a part. Various acute infections antedated the onset in most instances and the frequency of bronchial infections at this age suggests their importance as predisposing factors. In case 2 it is apparent that the condition was aggravated by acute infections. Fahr believed that infectious irritation was important in the majority of cases. Schultz, Wermbter and Puhl considered an infection of unknown type responsible in their case. Aschoff said that the question is still open, but he added that he could agree if Fahr should consider other unrecognized irritative factors. I shall discuss the relation of infection further in the section on animal experimentation.

About half of the generalized visceral forms of xanthoma have been considered as related in some way to icterus and disorders of the liver in general, diabetes mellitus or certain diseases of the kidney. It is important to note that in none of this group of cases have these conditions been present. In Griffith's patient there was jaundice, but it was without doubt secondary to the xanthomatous changes about the hilum of the liver as Griffith himself believed. In Fahr and Stamm's patient, death resulted from kidney complications, and lipoid changes were found in the kidneys.

Chambard early proposed a special diathesis for xanthoma; Arning and Lippmann regarded as "essential or idiopathic" those cases not associated with icterus, glycosuria or pregnancy. This applies especially to the juvenile form in which familial tendencies are frequently observed. So far as the group reported has been studied, there have not been clinical records of familial tendencies. The examinations of the blood in the members of the family in case 2, however, were suggestive. The mother had a blood serum cholesterol of 272 mg. per hundred cubic centimeters; one brother had a chronic valvular cardiac disease, and a single determination of cholesterol showed 175 mg. per hundred cubic centimeters of blood serum.

The clinical form which xanthoma assumes is considered as related to the intensity and persistence of the process, and I wish to add that it is also related to the age of occurrence. Usually the most extensive manifestations are found in subjects with a particularly elevated cholesterol. Especially in xanthoma diabeticorum, in which the cholesterol value generally is high, the eruption is apt to be extensive and frequently develops rapidly. On the contrary, under the influence of diet and, more strikingly, under the influence of treatment with insulin, the lesions often disappear, coincident with a decrease in blood lipoids.

In case 2, in which at the time of my first examination there was a moderate increase of blood cholesterol, x-ray examination showed moderate increase also in the destruction of bone. During the past year, while the blood cholesterol has been low, there has been a most remarkable lessening of the bone destructive process as shown by the roentgenograms. The defect in the bone at the vertex of the calvarium has filled in to such an extent that it can only be located with difficulty and the large areas at the base of the skull have been almost entirely regenerated. Coincident with this, the patient, instead of being irritable, is happy and active and is without pain or discomfort. He has increased in height 3½ inches, in contrast to his growth of less than 1 inch during the preceding twelve months, and the polyuria and polydipsia have decreased (compare *C* and *E* in figure 10).

Oppenheimer and Fishberg, observing the disappearance of extensive xanthoma in a young diabetic patient as the blood lipoid diminished under the treatment with insulin, stated that it proved for them the dependence of xanthoma on an excess of lipoids in the body fluids.

This is the generally accepted view, but cases have been reported by Arzt, Rosenthal and Braunish, Siemens and Dubs in which the two conditions were not present at the same time. These investigators considered the relationships between cholesterol in the blood and in the tissues as not essential. They explained the xanthoma manifestations either on the ground of local factors, mechanical and other irritations of the tissues, blood and lymph stasis and local inflammatory changes, or the influence of the chromaffin vegetative nervous system, such as an acquired biologic characteristic of cells, with respect to metabolism of cholesterin.

In regard to these negative observations, Levy expressed the opinion "that it is preferable to make note of these facts without trying to interpret them. Perhaps they will find an explanation in the doctrine of hypercholesterolemia, or on the contrary, they may put us on the track of factors which are still unknown."

The mechanism with which the body controls metabolism of cholesterol is complicated. Cholesterol in the blood undergoes great variations. In all metabolic disease individual symptoms undergo varied accentuations, so that there is no necessary parallelism between the picture of xanthoma and the increase in cholesterol. Cholesterol is only the starting factor. During the period in which the xanthoma remains stationary, the cholesterol is at a low level. In such instances, the association of xanthoma manifestations with increase in cholesterol is seen in the chemical structure of the lesions.

Hypercholesterinemia and Animal Experimentation.—A long series of animal experiments (by Anitschkow, Aschoff, Kawamura, Bailey,

McMeans, Chalatow, Zinzerling, Versè and others) furnish a most important confirmation of the clinical observations here discussed. They also demonstrate that pathologic degrees of hypercholesterolemia can be produced in animals by feeding diets rich in cholesterol, which suggests that there are new dietetic problems to consider in the feeding of infants and children.

Anitschkow, feeding rabbits on a diet rich in cholesterol, caused lipoid storage in the interstitial cells of the spleen, bone marrow, lymph nodes, Kupffer cells of the liver, walls of the large vessels and in extreme cases, in the connective tissue cells of the skin. He produced what in many respects could be regarded as an imitation of xanthoma in each of its many forms. These experiments confirm the clinical observation that lipoid storage varies with the duration and intensity of the process and that it occurs, preferably, in regions especially exposed to trauma and strain. They also demonstrate that under normal conditions lipoid is not stored in the presence of an aseptic irritative process but that it occurs when there is hypercholesterolemia. On the other hand, they demonstrate that lipoid storage appears in the presence of suppurative processes under otherwise normal conditions. In such instances, it results from the absorption of cholesterol locally liberated by the destructive effects of the suppurative process.

In another series of experiments, Anitschkow demonstrated that hypercholesterinemia, however transient, provokes lipoid storage. This confirms the fact that even though the subject may not at the time have hypercholesterolemia, xanthoma manifestations always indicate that it had been present at some former period.

Still another problem of clinical importance is explained by these experiments. Xanthoma is characterized by two processes, lipoid infiltration with the formation of xanthoma cells and connective tissue proliferation. For a long time, the succession of these processes has been in doubt. Some have regarded the lipoid infiltration as primary, while others affirmed that it is secondary to inflammation of the intima. According to Anitschkow, both views are right. On the one hand, the cholesterol grafts itself on previously injured surfaces, while on the other the lipoids acting on an artery which has been normal up to this time cause an irritative state and provoke a hyperplastic reaction. Zinzerling agreed that it does not require either injury or inflammation to bring about these changes, but that the irritating effect of cholesterol alone may produce the hyperplastic reaction.

These experiments demonstrated that lipoid storage (xanthoma manifestations) may appear in any part of the body in which there is activity of the cells. It extends to the interstitial tissue of the inner organs, suggesting an analogy to changes found in man. There may be a difference between what takes place in animal experimentation and

what actually occurs in pathologic changes in man; nevertheless, animal experimentation throws light on the nature of the condition as it is found in man.

The Reticulo-Endothelial System and Xanthomatosis. — Since Aschoff and Landow in 1913 proposed grouping certain body cells according to their functional properties rather than their morphologic characteristics, they have been called the reticulo-endothelial system. This cellular system, characterized by its exaggerated ability to ingest, is sometimes spoken of as a storage system or, since substances come from the blood stream and purification takes place, as a blood purifying system. Metchnikoff early studied the behavior of these cells. He differentiated between the circulating ameboid cells of the blood, the polymorphonuclear leukocytes, or microphages, and the relatively fixed ameboid cell of the tissues, or macrophages, and emphasized the highly phagocytic properties of the latter group. Possibly he had some notion of a special system; at any rate, he clearly appreciated the importance of these cells, not only in phagocytosis of foreign materials but in their part in processes of inflammation and immunity.

According to Aschoff, the reticulo-endothelial system is the intermediate agent of metabolism between the blood and the tissues. Besides playing a prominent part in metabolism, and especially in lipoid metabolism, it is probable that this system of cells is concerned in formation and destruction of blood, and that iron injected into the blood stream is stored in the reticulo-endothelial cells. It is also probable that the formation of bilirubin occurs within these cells. (See recent reviews by Aschoff, Sachs and Jaffé). While, as Oberling observes, this system is not a physiologic entity, as all of its elements do not behave in a similar manner and some authors hesitate to call it a system, nevertheless, a consideration of xanthoma manifestations and lipoid metabolism, in the light of this hypothesis, contributes much to the understanding of the pathogenesis and the microscopic changes as well as the clinical manifestations of xanthoma.

The experiment which particularly led to calling the special phagocytic cells a system was the work of Ribbert, who in 1904 demonstrated by injecting lithium carmine intravenously, intraperitoneally and subcutaneously that the coloring matter, although partly eliminated by the kidneys, was partly stored in certain cells of the organism and always in the same cells for a given organism. Ribbert also observed that the cells which were vitally stained were able to take up other substances injected into the blood stream, e.g., iron and lipoids. Aschoff made the first report of the investigations of his pupil, Kiyono, on the vital staining of these cells in normal and pathologic tissues. He introduced the term histiocyte to designate mesenchymal mononuclear phagocytic cells and described their behavior in detail.

Included in the reticulo-endothelial system are three main classes of cells, which are closely related genetically: (1) the reticulum cells of the splenic pulp, lymphatic tissue and bone marrow; (2) the endothelial cells of the liver capillaries, lymph sinuses, splenic sinuses, bone marrow, suprarenal capillaries and hypophyseal capillaries; (3) the phagocytic cells in the connective tissue, which include Ranvier's clasmatocytes of areolar tissue and Marchand's adventitial cells surrounding the blood vessels. Cells of this character may enter the blood stream, where they are present as monocytic elements (i.e., endothelial leukocytes of Mallory).

The essential microscopic characteristic of the varied xanthoma manifestations are the large bright foamy (xanthoma) cells. A question that has attracted much attention concerns the origin and nature of these cells. At one time, owing to a superficial resemblance, it was supposed that in some way they might be related to sebaceous gland cells. They have been regarded as a special kind of tumor cell and even a parasitic origin has been suggested. Most often, however, they have been considered as cells of endothelial origin showing a peculiar kind of fatty change. Pinkus and Pick, Aschoff, Pollitzer and Wile, Kawamura and Fahr observed that these foamy cells are of reticular and endothelial origin and possess phagocytic properties. Anitschkow, in his feeding of cholesterol to rabbits, definitely demonstrated their identity with the histiocytes by staining them vitally with pyrol blue and trypan red at the same time that he transformed them experimentally into xanthoma cells. He further demonstrated that the cells containing anisotropic bodies all belong to the reticulo-endothelial system. A review of the study of the microscopic changes shows that lipoid-containing cells (xanthoma cells) have been observed in all parts of the reticulo-endothelial system, and that they are extensively distributed in the group of cases I have described.

It is of interest to note that the same cells are the essential cells in the lesions of tuberculosis and in the lepra nodule and the specific lesion of Hodgkin's disease, the hyperplastic reaction resulting from different causes.

Whether the presence of lipoid in the cells is a sign of degeneration or of infiltration or whether lipoid is manufactured in the cell itself is still a much debated question. Virchow thought these fatty changes were a mark of degeneration. Kaiserling and Orgler, who first described double refractive bodies, observing them in the cells, believed that they originated there. Pick and Pinkus, Aschoff, Kawamura and Anitschkow, noting that the xanthoma cells have phagocytic properties, regarded the change as an infiltrative one. "It is not a passive one, however, as it is due to lipoidophagic activity on the part of the cells themselves" (*Weber*).

Even today there are different views regarding the presence of lipoids in the cells. Aschoff thought that the reticulo-endothelial cells had an especial affinity for lipoids. Heck recently expressed the opinion that the appearance of cholesterol in the tissues and its appearance in the blood have a common origin, but that at times they may occur independently of each other. For him, the fundamental principle of retention of cholesterin is a physiologic change in state, which differs in every case. As to a special cell affinity, as proposed by Aschoff, Fahr said that this is only a theory. Most of the recent observers regard the change as exclusively an infiltrative process, the truth of which is supported by animal experimentation. Oberling expressed the opinion that it is purely chemical, a view made acceptable by the present understanding of the reticulo-endothelial system.

Levy drew a striking analogy between the experiments of Ribbert and Anitschkow. "In both cases a colloidal substance injected into the veins of a rabbit is stored by a biologic system characterized by its elective phagocytic properties. In the two cases, moreover, the accumulation of phagocytosed substances, whether carmine or cholesterol, occurs with predilection in inflamed tissues or in tissues in an irritated state with tendency to proliferation. In a similar manner, the substances introduced into the skin of rabbits by Ribbert, Lebedew and Basten resulted in the formation of cholesterinophagic or carminophagic nodules which did not differ from one another, except in the nature of the substance injected." In conclusion, Levy observed "It is not too much to say that the xanthoma manifestations result from the 'vital staining' of certain parts of the reticulo-endothelial system by cholesterol esters and from the reaction this lipoid infiltration provokes."

GENERAL COMMENT IN RELATION TO THE SYNDROME

In view of the length of this study, I have not considered certain problems that are still unsolved. It is evident that there are no definite conclusions as to why lipoids accumulate in the body fluids. Abnormal congenital predisposition, as usually ascribed to the infantile group of this condition, is purely a supposition. There may be some hormone influence or disturbances of excretion, though these suggestions have not been proved. Physiochemical conditions are also considered as possible factors. Without doubt, alimentation plays a part, as hypercholesterinemia can be produced by types of nourishment. Lipoid metabolism has not been fully worked out, nor has its association with general metabolism been completely explained. Nevertheless, this consideration of Christian's syndrome, in connection with facts already in the literature, makes it possible for certain conclusions to be drawn

regarding the circulation of lipoids in the body fluids and the significance of this striking symptom complex.

The immense amount of microscopic and biochemical research on the subjects involved as well as the many points of interest in this unique syndrome make their consideration difficult.

The problems I shall consider are: (1) conclusions regarding the pathogenesis, (2) consideration of the conditions that should be included as manifestations of a general disturbance of lipoid metabolism, (3) the nature of the nodular lesions and finally, (4) consideration of clinical features in general.

CONCLUSIONS REGARDING PATHOGENESIS

All the varied xanthoma manifestations can be brought back to a single pathologic principle: the reticulo-endothelial system is infiltrated by certain substances. According to this interpretation, the change is essentially chemical. Lipoids and, in fact, all sorts of metabolic products, find particularly receptive cells in one part or another of the system, but lipoids, because of their physiochemical nature, are most often observed. The idea of an abnormal activity of the system in connection with lipoid metabolism is purely speculative. The change depends primarily on an increase of lipoids in the body fluids and secondarily on the duration of the condition of the blood and the local blood and lymph supply. A rise in the amount of lipoids in the body fluids or an increase through stasis may result in storage, and even after sufficient length of time, when the lipoid content of the fluids is so low as to appear normal, the lipoidophilic substance sometimes comes into view. Such factors as trauma and inflammation predispose to storage, and there are, without doubt, other undetermined factors; storage occurs when there is increased activity of the cells. Disturbances of circulation of the most varied kinds play a part, as is evidenced by the fact that a reversibility of the process with a decrease in hypercholesterolemia is occasionally observed. The tissues are not necessarily injured in becoming the seat of such a storage of fat, unless the secondary reactions in the lesions have already taken place. In general, the infiltration depends on the rise in amount of lipoid. Certain accessory factors predispose to localization, but hyperlipoidemia itself suffices to produce lipoid storage (xanthoma manifestations).

It is necessary to recognize that even though considerable, hyperlipoidemia does not always provoke lipoid storage. Although this fact does not permit one to doubt the certain rôle of hyperlipoidemia, it indicates that there are still unknown elements in the problem.

The biologic agents in the taking up of lipoid substances are the reticulo-endothelial macrophages. The chemical nature of the content of these cells is variable, and the extent of the infiltration differs in

each case. When it is more in the skin, it is less evident in the internal organs and vice versa, or even when more in one organ, it is less in another.

One can assume that, depending on the reactive state of the individual, the reticulo-endothelial macrophages appear at one time as an actively evolving diffuse process, and at another, grouped in the form of slowly developing nodular growths. The behavior of excess lipoids circulating in the body fluids recalls in many ways a relationship to other metabolic processes. The comparison with gout caused by uric acid and gout caused by calcium is suggestive.

CONDITIONS THAT SHOULD BE INCLUDED AS MANIFESTATIONS OF A GENERAL DISTURBANCE OF LIPOID METABOLISM

A review of the literature shows that there is no agreement as to what conditions should be included as the manifestations of a general disturbance of lipoid metabolism. The cases of xanthoma of the eyelid are separated from the multiplex group. The cases of glycosuria are considered by themselves; the tuberous and tendon sheath varieties are sometimes studied in connection with dermatologic investigation, and again as unrelated conditions in surgical or pathologic literature. Those developing before puberty are separated from cases developing at a later period, and the generalized forms are frequently described as separate conditions.

According to several investigators, however, there is no essential difference between xanthelasma palpebrarum, xanthoma multiplex and generalized xanthoma, and Niemann's disease and Gaucher's disease are regarded as related conditions.

The relatively large series of cases here described in which hyperplasia of the lipoid cells was present, both in the inner organs and as localized nodular lesions arising from white fibrous connective tissue, makes it possible to consider them as a sort of connecting link which unites these different forms.

Clinical observations as well as microscopic changes appear to justify the consideration of Niemann's disease as the widespread, rapidly developing infantile type of this disturbance of lipoid metabolism. It is possible that with further knowledge concerning lipoid metabolism and its relation to general metabolism, Gaucher's disease may also be included in this grouping. Its similarity to Christian's syndrome supports this view. Gaucher's disease appears to be the same condition infiltrated with more complex lipoproteins.

In regard to cases associated with icterus and diseases of the liver and certain diseases of the kidney, this study suggests that these symptoms may be secondary to the lipoid hyperplasia and also represent the manifestations of a primary disturbance of lipoid metabolism. The

cases showing glycosuria and diabetes mellitus fall into the same grouping only modified by the associated disturbance of carbohydrate metabolism. It may be that the disturbance in carbohydrate metabolism, in such cases, results from the hyperplasia of the lipoid cells. It has repeatedly been observed that diabetes mellitus is invariably associated with a disturbance of fatty metabolism and that glycosuria has sometimes been known to appear after, as well as before, the occurrence of the xanthoma manifestations.

These observations indicate that there are still other conditions that can be brought into this relationship—at least some of the group now classed as multiple myeloma and a scattered series of cases, unidentified as to etiology, which have been described in the literature.

The clinical manifestations, the microscopic changes and the chemical content of the lesions show great variations, but all these conditions represent the same irritative proliferation of connective tissue elements (i.e., reticulo-endothelial hyperplasia resulting from the infiltration of lipoids), their only difference being in the nature of the lipoids concerned. The manifestations vary in clinical form according to the rate of development, the duration of the process and the age of occurrence.

The clinical conditions which can be brought together as primary disturbances in lipoid storage of the reticulo-endothelial system are:

Xanthelasma palpebrarum, a slowly developing form usually occurring in adults.

Xanthoma multiplex and its varieties representing a more acute process occurring frequently in early childhood.

So-called xantho-myeloma of the tendon sheaths occurring at all ages but usually in young adults.

Generalized visceral xanthoma-xanthomatosis, including Christian's syndrome, occurring especially in early childhood.

Niemann's disease, the rapidly developing generalized form, in infancy.

Xanthoma diabeticorum, a form modified by a disturbance of carbohydrate metabolism, in which the disturbed carbohydrate metabolism may prove to be secondary to the hyperplasia of the lipoid cells.

Gaucher's disease, perhaps modified by a disturbance of protein metabolism, in which case the disturbed protein metabolism may also prove to be secondary.

Concerning the cases now classed with multiple myeloma and certain unidentified cases scattered through the literature, further study would be necessary to determine which of these should be included in this group.

THE NATURE OF THE NODULAR LESIONS

In this syndrome the lesions that are most notable morphologically are the yellow to yellowish brown nodular lesions. In the fourteen cases here described, these tumor-like forms were numerous, appearing to arise from the white fibrous connective tissue of the dura, peri-

osteum, peritoneum and pleura, and rarely in the interstitial tissue of certain organs. The histologic examination showed that they were characterized by the presence of lipoid-containing cells and great variability in structure. In one part, they had angiomatous characteristics; in another, they gave the appearance of a fibroma, and through extensive differentiation seemed to suggest a granuloma form; frequently, the picture gave the impression of true mesenchymal giant cell sarcoma.

Various significances have been suggested for these nodular lesions. They have been regarded as tumors of the connective tissue, secondarily infiltrated with lipoids; as special tumors developing from xanthoma cells; as granulomas developing from the occurrence of an inflammation of undetermined nature, having provoked the local fixation of the excessive lipoids circulating in the blood, or as granulomas which have become xanthelasmic as a result of a degenerative process and which have liberated the constitutional cholesterin locally.

As recently as 1924, in discussing the autopsy of the patient originally described by Griffith, Wiedman and Freeman stated that "the presence of 'xanthomas' (nodular lesions) in the viscera in this case is to be accounted for on the basis of coincidence, one moiety being a granuloma of an undiagnosed disease, and the other the result of hypercholesterolemia."

The constant symptoms in this series of cases indicate that all the different lesions, diffuse and nodular, are a part of the same pathologic process. They have a common etiology—hyperlipoidemia.

In spite of the fact that the nodular lesions, by their size and tissue structure, frequently give the impression of true neoplasms and sometimes of tumors of the granulation tissue, they are not real tumors. Their distribution does not necessarily correspond with hematogenous metastases, and their lack of an infiltrative destructive character, shown by their avoidance of vital tissue, distinguishes them from the true neoplasms. Their long continuance of development, suggestively symmetrical distribution and occasional retrogression indicate a systemic process rather than an autonomous growth.

To understand the nature of these tumor-like nodules, one must consider them from their clinical and developmental side as well as from their histologic structure. If one takes into account their relationship to the reticulo-endothelial system, the process is made clear and their development may be summed up in the following manner: The constant presence of ("foreign body") excess lipoids in the blood stream causes an irritation of the vessel walls, whereupon a perivascular cell infiltration takes place. At first, small round lymphoid cells with little protoplasm appear; then, by splitting of the vessel walls, fusiform cells with an abundance of protoplasm develop, and finally, owing to

fusion, multinuclear xanthoma cells are formed. These cells show a common vessel endothelial origin and all contain lipoids, the older and more mature cells containing the greater amount. They vary in form and size, but their nuclear structure is similar and they never show karyokinesis. The youngest cells are always in the center of the lesions near the blood vessels and the older and more mature xanthoma cells nearer the periphery.

The cells of the reticulo-endothelial system are in constant renovation which is stimulated by "blockage"; that is, when the cells are loaded with a given substance they become refractory to all other substances and so stimulate the demand for more cells (Kiyono). The nodular lesions under consideration are the result of perpetual blockage. The histiocytes, being immediately filled by lipoid from the body fluids, become refractory to all other substances and so stimulate the demand for more cells, which in their turn become loaded, and repeat the process provoking the continuous increase in the new formation. Thus, the xanthoma nodule does not increase by multiplication of its cell elements, but by the addition of new cells.

The characteristic xanthoma cells are not always observable in the lesions. This and the fact that the lesions sometimes retrogress or recur after excision is explained by their biologic nature. One is not dealing with true neoplasms, but with hyperplastic new formations, i.e., lipoid storage tumors. The formation of these nodules is a compensatory act on the part of the body in its attempt to rid the blood of an excess of lipoid which cannot be properly excreted.

These views, confirmed by the experimentation of Anitschkow and Kuczynski and by the studies of microscopic changes by Wustmann and Weber and others, are of interest clinically as they bring into relationship with this pathogenesis a long series of, perhaps rare, new formations arising from the dura, periosteum, pleura, pericardium, peritoneum and endosteum, as well as from the tendinous, peritendinous and periarticular surfaces and fascia. To the clinician this is important as it decides their benignancy or malignancy and so determines the manner of treatment. Broders, in describing the latter group under the title "Benign Xanthic Extra-Periosteal Tumors of the Extremities Containing Foreign-Body Giant Cells," remarked that they masquerade under various names: sarcoma, myeloid sarcoma, myeloid endothelioma, myeloxanthoma, granuloma, giant cell tumor and giant cell sarcoma.

The bone destruction associated with these nodular lesions, in the cases I have described, is a notable clinical feature. In every instance the cranial bones had suffered the most, but the roentgen-ray studies demonstrated similar, though less extensive, defects in the flat bones of the pelvis, rarely the scapulae, ribs and vertebrae, and in one instance,

in the femur and humerus. Usually, thickening or evidence of bone regeneration were not found. The bony structure adjacent to the defect appeared normal, according to the x-ray studies, as did all the other bones in the body. One of Schüller's cases showed a lessening of bone destruction and improvement in the general condition. In case 2 of my own, the roentgenograms showed a surprising decrease in bone destruction (compare *C* and *E* in figure 10).

The presence of true foreign-body giant cells in the lesions, in association with pressure, suggests an explanation for this bone destruction. Such changes have been observed in other types of xanthoma by MacLeod, Merrill and Broders. It also occurs in other pathologic conditions in which there are foreign-body giant cells.

An early symptom observed in the majority of these cases was an irritated condition of the gums and a loosening of the teeth. This was usually first indicated by the loosening of the back molars of either jaw. The teeth themselves appeared normal, except for the erosion of some of the cusps, which was similar to the destruction that takes place in the bones. This condition resulted from the xanthoma nodules arising from the periosteum covering the maxillary bones. There were many foreign-body giant cells in these tumor-like masses with the same bone destruction evident. These lesions are of interest in connection with the study of giant cell epulis of the jaw and its etiologic relationship to xanthoma.

The extent of this paper does not permit me to discuss further this problem in which there is so much interest at present, but I wish to repeat that these new formations should be considered from the standpoint of their development, as well as from their pathologic structure. This study indicates that certain yellow to brown, lipoid-containing, so-called endotheliomas, angiomas and giant cell fibrosarcomas of the dura, periosteum, pleura and peritoneum are hyperplastic new formations. The lipoid in these nodules suggests the irritant which produces them, and so separates them from the field of true autonomous growths.

Local liberation of lipoids can cause the formation of cholesterin granulomas. Various inflammatory and suppurative processes, as well as mesenchymal tumors, can complicate themselves by secondary lipoid infiltration. The tumor-like lesions I have described I regard as due, primarily, to a disturbance of lipoid metabolism. The fact that the nodules sometimes occur singly does not necessarily separate them from the generalized group, but it indicates that there may be secondary factors, such as trauma, irritation or infection, which determine their localization. Wustmann spoke of these single forms as "storage organs." According to this view, the essential factor in their production is also the excess of lipoids in the body fluids.

CLINICAL FEATURES IN GENERAL

The fourteen cases I have considered all occurred in early childhood. Six of the patients were girls and eight were boys. In ten cases, the probable onset occurred during the second year of life, with one each in the third, fourth, sixth and seventh year. The onset was insidious and periodic, so that in most instances the disease was quite advanced before a physician was consulted.

The family histories, so far as they were studied, did not show any unusual features, with the exception of that in case 2, in which one brother had chronic valvular disease and the mother hypercholesterinemia. The obstetric histories were normal and the births uneventful. During the first year, nutritional disturbances did not occur and development was normal. The blood Wassermann reactions were negative, and tuberculosis was not present. One of the common infectious diseases which frequently occur at this age—measles, mumps, whooping-cough or scarlet fever—antedated the onset in most instances. In both of my cases, a history of trauma was associated with some of the bone defects. It was also mentioned in one of Schüller's cases.

The symptoms depended on the location of the lesions, the extent of involvement and the mechanical effects resulting from pressure and bone destruction. A notable lack of subjective symptoms was apparent, but during the active stage there was frequently increased irritability and often tenderness and pain referred to the lesions.

The occurence of diabetes insipidus in all of the series, except in one of Hand's patients and in one of my own, is perhaps the most notable clinical feature of the group. In reviewing the literature I have been able to collect reports of eighteen cases of xanthoma, including those I have reviewed, in which there were lesions at the base of the brain surrounding the hypophysis and occasionally involving the posterior lobe of the pituitary, with symptoms of polyuria and polydipsia. The problem which this suggests, as well as various other questions, must remain for further study. But, according to my present belief, these pathologic changes do not determine whether diabetes insipidus is due to pressure and irritation at the base of the brain, or to lesions involving the posterior lobe of the pituitary but, rather, that it may be due to either cause.

It is of interest to note that in case 1 the roentgenogram showed extensive destruction at the base of the brain involving the sella turcica, and that at autopsy yellow masses were found, filling the sella and surrounding the hypophysis. In this case symptoms suggesting diabetes insipidus had not developed. This is surprising when one considers the extent of the nodular lesions, but suggests that the bone erosion may account for the lack of pressure symptoms. If the dia-

betes insipidus is due to pressure at the base of the brain, which is the most commonly attributed cause, it would account for the intermittence of these symptoms and explains why, as in case 1, polyuria and polydipsia do not always develop in the presence of extensive local changes.

While instances of diabetes mellitus were not found in the series, the case reported by Fahr and Stamm was regarded as an atypical diabetes mellitus and the patient had intermittent glycosuria. I believe that the condition is closely related to this group and that the patient probably had diabetes insipidus. A clinical relationship between diabetes insipidus and diabetes mellitus has long been observed. This again suggests that the diabetes mellitus in these cases may be secondary to the lipoid hyperplasia or to the resulting lipoid changes in the reticulo-endothelial portion of the pancreas (and possibly other glands).

Retardation in growth was apparent in most instances from the onset of active symptoms. In case 2 normal growth returned with general improvement. In the two older members of the group (see cases reported by Schüller and Kyrklund), besides dwarfism, a typical dystrophia adiposogenitalis developed. They were both active progressive cases. Kyrklund's patient also showed retardation in mental development, as did most of the cases in the infantile group first described by Niemann, and many of those classed as Gaucher's disease. It is a question whether this far reaching process, which involves the reticulo-endothelial system, is not in some way causally related to the mental retardation as well as to the retardation in growth.

Because of the retardation in growth and the diabetes insipidus, Christian and Schüller regarded the "syndrome" as probably due to a disturbance of pituitary function. Various observers explain disturbances of lipoid metabolism as a function of certain endocrine glands (Goldzieher and Hirschhorn). I believe this study suggests that the metabolic disturbance is primary and that the lipoid infiltration in these glands, the pressure effects from the nodular lesions or unknown factors (possibly blockage by lipoids and other pathologic metabolites) definitely related to the pathologic condition account for their disturbed function; that is, the pathologic changes in these cases indicate that the abnormal hormone action is sometimes secondary to the cellular hyperplasia in the glands. This view is directly opposite to the one generally expressed and is suggestive in regard to the part cellular reactions of the reticulo-endothelial system may play in other so-called endocrine disturbances.

A chronic otorrhea occurred in case 1, evidently from involvement of the mastoids by this process. The same condition occurred in several other cases in the series in which mastoid operations were per-

formed. In two instances there was involvement of some of the nasal sinuses, which suggested a rare and new pathologic change for these conditions.

The varying degrees of exophthalmos, which occurred in every instance, may be explained by the bone destructive process. Possibly the size of the nodular lesions in the orbit was a factor, but these changes did not produce sufficient pressure to cause optic atrophy. The fundi in every patient examined were normal.

Various other well recognized clinical conditions may be explainable on the basis of lipoid hyperplasia of the reticulo-endothelial system: atheroma, especially of the valves of the heart and larger vessels; certain types of cirrhosis of the liver; "strawberry gallbladder"; occasionally cholelithiasis; certain forms of nephrosis, myelin kidney representing an extreme form; osteitis fibrosa; arcus senilis; certain familial forms of Dupuytren's contracture and cholesteatoma of the choroid plexus.

Lesions of the skin suggesting xanthoma were not found in any of the group here described, with the exception of Hand's second case which resembles the clinical picture of the eruption of juvenile xanthoma of the rapidly developing congenital type. Thus, the clinical observation made by Lubarsch, that when the eruption occurs more in the inner organs less is found on the skin, held true.

In regard to the blood changes in the syndrome, too few examinations were made for any conclusions to be drawn but the observations are of interest. Manifest lipemia was not observed in any instance. There was usually a slight degree of anemia with a moderate increase in leukocytes, this increase sometimes being due to a large mononuclear excess (histiocytosis). In Christian's case, the leukocyte counts varied from 6,600 to 20,100. In my first case, two leukocyte counts were 17,350 and 17,600, respectively. The differential counts were: polymorphonuclears, 64 per cent; large mononuclears, 32 per cent; small lymphocytes, 4 per cent, and polymorphonuclears, 73 per cent; large mononuclears, 20 per cent; small lymphocytes, 7 per cent.

In the patient of Schultz, Wermbter and Puhl, the blood changes were such an outstanding feature that at first they believed they were dealing with a case of anemia pseudo-leukemia infantum (von Jaksch anemia). Evidence of a blood destructive process was not found, but this severe anemia was due to the hyperplasia in the long bones interfering with blood formation. The bone marrow was slightly involved in most of the series, but in this case the involvement was extensive.

The lipoid cell hyperplasia of the hematopoietic apparatus suggests problems for future study in connection with the explanation of certain, apparently confusing, blood pictures. In the case just mentioned, it is evident that the anemia varies with the extent of the hyperplasia involving the bone marrow. A leukemia of histiocytic origin could

also complicate this condition, and these two blood changes might occur at the same time, making the interpretation of the examinations of the blood difficult. Kiyono explained why the histiocytes do not appear more often in the peripheral circulation. The large cells, because of their size, are caught in the pulmonary capillaries and so rarely appear in the peripheral circulation.

Four of the group came to autopsy. In all the fatal cases, there was pulmonitis with an extreme degree of pulmonary fibrosis, which represented a rare type of pathologic change in the lungs. This change is of interest as it suggests the important part played by the lungs in lipoid metabolism. Experimentation indicates that the pulmonary tissue is concerned in the destruction of fats. Aschoff regarded the lungs as a sort of digesting organ for lipoids and fats. It may be that the pathologic change causing a stasis of lipoids, as Lubarsch suggested, is a factor in determining the clinical form the group presents; it certainly is a deciding factor in the prognosis.

In the group described there have been seven deaths, and so far as is known, the remaining seven patients are still living. Two, at least, have shown improvement, indicating that the prognosis is better than the clinical symptoms would seem to suggest.

The tentative diagnosis, in most instances, was some form of tumor of the brain, but without exception there was an entire absence of neurologic symptoms or signs suggesting cerebral pressure. It is of clinical interest to remember that the nodular lesions arising from the dura and periosteum with erosion of the bone do not usually cause pressure symptoms. The rarely occurring cutaneous lesions in the generalized visceral forms have the same diagnostic significance as tophi in gout. A yellow coloration of the skin, frequently present in this condition, would also be of diagnostic importance. The varying degrees of exophthalmos and the noticeable tendency to dwarfism give most of these children a facies and "froglike" appearance which is nearly typical of the condition.

There should not be any difficulty in the clinical diagnosis of the syndrome. In any case of bone defects, especially of the cranium, polyuria, polydipsia, exophthalmos, even of loose teeth, dwarfism and dystrophia adiposogenitalis, this condition of disturbed lipoid metabolism should be considered. It is important to remember that the blood serum does not always show an increase in lipoids and that various kinds of lipoids are concerned in this process.

Regarding treatment, the pathogenesis of hyperlipoidemia suggests possibilities of rational procedure to the internist. It is generally agreed that hyperlipoidemia can be produced by types of nourishment. Animal experimentation shows that the cholesterol content of the blood is easily influenced by the cholesterol content of the food. While the

juvenile form I have described is frequently regarded as idiopathic, this view is theoretical. From the clinical standpoint, it appears permissible to consider this metabolic disturbance as in the nature of a diet disease—not a deficiency disease, but rather the result of certain kinds of food excess. "Excess of albumins, as well as of lipoid-containing foods, brings forth a true lipoid reaction" (Aschoff). It is also evident that infections and toxic states aggravate the condition (Fahr).

This view brings a long series of pathologic conditions into the realm of internal medicine. According to Rothschild and Rosenthal, the dietetic treatment of persons with hypercholesterolemia consists in diminishing the intake by using foods of low cholesterol content and by rendering absorption as difficult as possible. A diet low in fat content they believed answers both purposes. In cholelithiasis, they have found effective the giving of a fat-free diet for three or four days, alternating this with a more liberal but low fat diet.

In case 2 with restriction in lipoid-containing foods, a diet consisting of a moderate amount of protein and green vegetables, and the giving of desiccated thyroid and anterior lobe pituitary by mouth, along with intelligent hygienic care and dental prophylaxis, the blood cholesterol has decreased from 317 mg. per hundred cubic centimeters in 1926 to 111 mg. in 1927. Coincident with this change, there has been a remarkable improvement in the general condition, a return to a normal rate of growth, a lessening in the polyuria and polydipsia and a notable decrease in the bone destructive process, as shown by the roentgen-ray studies. The symptoms in this single case, however, are only regarded as suggestive.

For a long time it has been observed that persons with xanthoma diabeticorum respond to dietetic treatment and recently that the condition is still more promptly influenced by the use of insulin. Some observers have not found insulin generally effective in the group I have described (Ingram), but one can feel hopeful that a successful dietetic rationale will be devised for this (diet) disease.

SUMMARY AND CONCLUSIONS

Two new cases of the striking syndrome "defects in membranous bones, exophthalmos and diabetes insipidus," one in which a study was made at necropsy, the other in which the patient is still under clinical observation and shows a remarkable improvement in general condition, are here reported and discussed with twelve other reports of cases collected from the literaure.

These fourteen cases, all occurring in early childhood, have been brought into relationship with other similar cases already recognized as xanthoma. In this study the clinical picture, the microscopic changes and the pathogenesis have been considered, and their relation to the reticuloendothelial system has been discussed.

All these cases represent a form of generalized visceral xanthoma-xanthomatosis in which many parts of the reticulo-endothelial system show lipoid storage or lipoid cell hyperplasia. This occurs as a diffuse process in the interstitial cells of various organs, especially the lungs, liver, lymph nodes, bone marrow and spleen, as well as in hyperplastic nodules arising from the areolar tissue, particularly of the dura, periosteum, pleura and peritoneum. This pathologic change, diffuse and nodular, is regarded as the manifestation of a disturbance of lipoid metabolism.

Although with the present limited knowledge of lipoid metabolism and its relation to general metabolism positive deductions cannot be drawn, the consideration of these cases in connection with facts already in the literature, especially the part played by the reticulo-endothelial system, seems to justify certain general conclusions.

According to my present interpretation of this process, lipoid and various other substances in excess in the body fluids become pathogenic for the organism. There is at first an irritation of the vessel walls; then perivascular cell infiltration takes place, the lesions increasing as a result of the progressive blockage of the reticulo-endothelial system. This hyperplastic reaction represents a compensatory act on the part of the body and is its attempt to rid its fluids of substances that cannot be properly excreted and that act as irritants. Trauma or inflammation may account for the special localization in these cases or there may be some other factor not as yet determined. It occurs in the places in which there is increased cell activity in the presence of hyperlipoidemia.

Abnormal congenital predisposition has usually been ascribed as the cause of the excess lipoid in the body fluids, but this has not been proved. Whether this condition represents a congenital or acquired familial or nonfamilial derangement of lipoid metabolism must await future study. This condition, however, may prove to be a diet disease in the same sense as are uric acid gout and calcium gout.

As this investigation has been made from the clinical point of view, I shall call special attention to certain features of general medical interest.

The relatively large series of cases here described constitute a group which brings together other lipoid metabolic diseases of the reticulo-endothelial system. Niemann's disease is the rapidly developing generalized xanthoma of infancy, while Gaucher's disease represents a similar condition with an infiltration of more complex lipoproteins, and this study suggests that in the cases associated with diabetes mellitus or glycosuria, icterus and disorders of the liver and certain diseases of the kidney, these symptoms are secondary to the lipoid cell hyperplasia and are also the result of primary disturbance of lipoid metabolism. Each of these conditions differs in clinical form, in the pathologic structure of the lesions, and in the nature of the lipoids

concerned, but they all represent the same irritative proliferation of connective tissue elements—reticulo-endothelial hyperplasia; i.e., there is no essential difference between xanthoma in all its many forms, Niemann's disease and Gaucher's disease. They all are manifestations of the same pathologic process, perhaps modified by certain differences in the patient's general metabolic state.

The bone destruction, exophthalmos, diabetes insipidus, dwarfism and infantilism often present and frequently regarded as evidence of disturbed pituitary function are the results of this pathologic change. The same cause can be assigned for the less often observed dystrophia adiposogenitalis, for certain confusing blood pictures and other well recognized conditions.

My conclusion that the pituitary dysfunction results from the lipoid cell hyperplasia is suggestive concerning the part various cellular reactions of the reticulo-endothelial system may play in other so-called endocrine diseases. Such a hypothesis gives a definite pathologic-anatomic basis for, and explains the correlation of, certain disorders of the ductless glands.

That the nodular lesions with their varied pathologic changes (sometimes in a late stage of development not even showing foam cells) are hyperplastic new formations gives support to the opinion that a considerable number of yellow to yellowish brown lipoid-containing so-called endotheliomas, angiomas, giant cell fibrosarcomas of the dura, periosteum, pleura and peritoneum are not autonomous growths but lipoid storage tumors.

The recognition of the fact that the varied symptomatology is caused by the pathologic change resulting from hyperlipoidemia is important, since in this manner can be explained the pathogenesis of a number of other obscure conditions, and methods of treatment for all these conditions are suggested.

Finally, this lipoid metabolic disease of the reticulo-endothelial system—lipoid gout—when viewed in all its many forms, is by no means a rare condition.

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SYNOVIAL FLUID IN CHRONIC ARTHRITIS

BACTERIOLOGY AND CYTOLOGY *

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The object of these studies on chronic arthritis has been to correlate the bacteriology and cytology of synovial fluid with the clinical aspects of the disease. The anatomy and physiology of the cellular elements were studied by the supravital method of staining living cells. An endeavor was made to ascertain whether there is any difference between the cytologic observations in sterile synovial fluid and in that from which positive cultures of bacteria are obtained. There is no account in the literature of a correlation of these factors.

Considerable attention has been given in the literature to the bacteriologic and clinical aspects of both acute and chronic arthritis. Cytologic studies of the synovial fluid have been considered in less detail and rather inadequately. We had hoped that this would have some bearing on the cultural observations, and that a positive joint culture could be predicted from the number and types of cells found. Studies of syphilitic, tuberculous, acute septic and traumatic types of arthritis are not reported. The data presented were accumulated by the study of sixty-three cases of chronic arthritis. The cases were seen in the wards and in the outpatient department of the Johns Hopkins Hospital during the year 1926-1927.

CLINICAL STUDY

The cases studied, as determined by clinical and roentgenologic evidence, included fifty-two of the infectious type, nine of the hypertrophic type and two of the infectious and hypertrophic type. These cases presented various degrees of clinical activity, manifested by swelling, tenderness, stiffness and increase in local heat of the joints. There were fifty-four cases of multiple joint involvement, and nine cases of single joint involvement. In the latter group, two patients had localized arthritis in the hip joints, and seven had localized arthritis

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in the knee joints. An analysis of the cases as to sex showed that 54 per cent were in men and 46 per cent were in women. This percentage is essentially the same as that found by Billings, Coleman and Hibbs [1] and by Pemberton and Pierce.[2] The former, in 411 cases, reported 59 per cent in men, and 41 per cent in women, while the latter reported 700 cases with 69 per cent in men and 31 per cent in women. The patients varied in age from 15 to 72 years. The average age was 43.

TABLE 1.—*Analysis of Probable Source of Infection in Sixty-Three Cases of Chronic Arthritis*

Probable Sources of Infection	No. of Cases	Per Cent
1. Throat without history of acute tonsillitis	23	38.9
2. Infected tonsils	14	23.7
3. Prostatitis	7	11.8
4. Infected sinuses	4	6.8
5. Abscessed teeth or pyorrhea	3	5.1
6. Urethritis	3	5.1
7. Gastro-intestinal tract	2	3.4
8. Uterine cervicitis	1	1.7
9. Pyelitis and cystitis	1	1.7
10. Infected toes	1	1.7

The duration of the disease varied from one month to sixteen years. The average duration was three years.

Particular attention was paid to the probable source of infection. An analysis of the most likely foci of infection in the sixty-three cases is recorded in table 1.

In four of these sixty-three cases the probable sources of infection could not be determined. Two were thought to be partly metabolic in origin. In the nineteen cases in which organisms were grown from the

TABLE 2.—*Probable Sources of Infection in Nineteen Cases of Chronic Arthritis in Which Organisms Were Grown from Joints or Regional Lymph Nodes*

Probable Sources of Infection	No. of Cases	Per Cent
1. Throat without history of acute tonsillitis	8	42.1
2. Infected tonsils	5	26.3
3. Infected sinuses	2	10.5
4. Prostatitis	2	10.5
5. Cervicitis	1	5.3
6. Urethritis	1	5.3

joints or regional lymph nodes, the probable sources of infection were as recorded in table 2.

Reports of these nineteen cases are given at the end of the paper.

1. Billings, F.; Coleman, G. H., and Hibbs, W. G.: Chronic Infectious Arthritis: Statistical Report with End-Results, J. A. M. A. **78**:1097 (April 15) 1922.

2. Pemberton, R., and Pierce, E. G.: Clinical and Statistical Study of Chronic Arthritis Based on 1,100 Cases, Am. J. M. Sc. **173**: 31, 1927.

BACTERIOLOGY OF JOINTS AND REGIONAL LYMPH NODES

Schüllen,[3] in 1893, described a small bacillus which he obtained by culture on gelatin bouillon of joint fluid from patients with chronic rheumatoid arthritis, and which, when injected in dogs, produced arthritis.

Blaxall,[4] in 1896, found in the synovial fluid of rheumatoid arthritic joints, and occasionally in the blood, a minute bacillus. It possessed marked polar staining, was decolorized by Gram's method, and could be stained only by prolonged immersion in aniline-methylene blue. Inoculation experiments failed.

Poynton and Paine,[5] in 1902, who had previously found a diplococcus or short streptococcus in patients with acute rheumatism, isolated a similar organism from an osteo-arthritic joint, which produced arthritis when injected intravenously into rabbits.

Rosenow,[6] in 1914, stated that in cases of arthritis deformans he found the same organism in regional lymph nodes as in the joints, but he did not cite any examples. He made cultures of regional lymph nodes in fifty-four cases of chronic arthritis. In thirty-two instances he recovered nonhemolytic streptococci; in fourteen, *B. welchii;* in five, staphylococci; in five, diphtheriods; in three, *B. mucosus;* in one, *Micrococcus catarrhalis*; in one, gonococcus, and in seven, no growth.

Bloomfield,[7] in 1915, studied the bacterial flora of lymph nodes. He employed in this study seven normal and twenty-five pathologic nodes. In a high percentage of cases, organisms could be grown more often in diseased than in normal nodes. The organisms obtained were saprophytes, identical with, or closely related to, the surface flora of the body. Bloomfield suggested that these organisms constitute, perhaps, a more or less permanent flora of lymph nodes. None of the twenty-five strains isolated could be shown to be the cause of specific diseases.

Billings, Coleman and Hibbs,[1] in 1922, made cultures of regional lymph nodes in twenty-eight cases of chronic infectious arthritis. In one case they isolated a hemolytic streptococcus; nineteen cases showed green, nonhemolytic streptococci, and one revealed a mixture of hemo-

3. Schüllen: Untersuchungen über die Aetiologie der sogen. chronisch-rheumatischen Gelenkentzündungen, Berl. klin. Wchnschr. **30**:865, 1893.

4. Blaxall, F. R.: Rheumatoid Arthritis: Its Clinical History, Etiology, and Pathology, Lancet **1**: 1120, 1896.

5. Poynton, F. J., and Paine, A.: Reports of the Pathological Society of London. Brit. M. J. **1**: 79, 1902.

6. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Specific Methods, J. A. M. A. **63**: 905 (Sept. 12) 1914.

7. Bloomfield, A. L.: The Bacterial Flora of Lymphatic Glands, Arch. Int. Med. **16**: 197 (Aug.) 1915.

lytic and nonhemolytic streptococci. Joint cultures were made in fourteen cases. In five of these, green, nonhemolytic streptococci were cultivated, and in one a mixed hemolytic and nonhemolytic streptococcus growth was obtained.

Boots and Cullen,[8] in 1922, studied the hydrogen ion concentration of joint exudates in its relation to infection. They found an acid reaction in one case of infection with *Staphylococcus aureus*, and in one case of infection with *Streptococcus hemolyticus*. In cases of rheumatic fever and arthritis of undetermined origin, the p_H of the synovial fluid approximated that of the blood.

Holman,[9] in a recent review, discussed the subject of focal infection and elective localization. Reference should be made to this paper for a more detailed account of the rôle of focal infection in pathologic processes.

All our cultures were made by planting the synovial fluid in blood beef infusion broth at p_H 7.4 and on blood beef infusion agar at p_H 7.4. Deep cultures were made with ascitic fluid dextrose—beef infusion agar, p_H 7.4. Cultures were planted on ascitic fluid dextrose agar, the tops of the latter tubes were heated to force out the oxygen, and a rubber stopper was inserted immediately. Similar procedures were used for lymph node cultures when these were made. Table 3 gives the results in the positive cases.

In all, cultures were made of the joint fluids of sixty-three patients, with the recovery of organisms in fourteen, or 22 per cent. In some of the positive cases, repeated punctures and cultures were made, giving a total of twenty-one bacteriologically positive joint fluids. Eleven of the joint cultures contained *Streptococcus viridans*, two gonococci and one *Staphylococcus aureus*.

Regional lymph nodes were excised or punctured, and cultures made in twenty-one of the sixty-three cases.[10] There were ten positive growths, or 48 per cent. Of the ten positive growths, nine were of *Streptococcus viridans* and one of gonococcus. In five of these cases, there were positive joint cultures, the same type of organism being grown from the joint and the lymph node.

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8. Boots, R. H., and Cullen, G. E.: The Hydrogen Ion Concentration of Joint Exudates in Rheumatic Fever and Other Forms of Arthritis, J. Exper. Med. **36:** 405, 1922

9. Holman, W. L.: Focal Infection and "Elective Localization," Arch. Path. **5:** 68 (Jan.) 1928.

10. For a number of years in the Johns Hopkins Hospital Clinic, lymph nodes have been removed for culture in chronic arthritis. Stimulation for part of this work was obtained from experience with these cultures and contact with Dr. W. S. Baer, Professor of Orthopedic Surgery.

Reference to tables 3 and 4 will show the cell counts in most of the positive cases. The relationship between the increased cell count and the positive cultures is discussed under the heading Cytology.

From these bacteriologic studies, it is apparent that positive cultures can be obtained in joint fluids and regional lymph nodes in a fair per-

TABLE 3.—*Results of Positive Cultures of Synovial Fluid*

Case	Joint	Lymph Node	Organism	Growth	Incubation Period, Days	Degree of Clinical Activity	Probable Focus	Duration of Arthritis, Years
1	Left knee	.....	S. viridans	Light	1	++	Throat	2
2	Right knee	.....	S. viridans	Light	3	+++	Tonsils	5
3	Left knee	.....	S. viridans	Light	3	++++	Tonsils	½
4	Left knee	.....	S. viridans	Light	2	++++	Cervix	10
		Right inguinal	S. viridans	Light	2			
5	Right knee	.....	S. viridans	Light	6	+++	Throat	2
		Epitrochlear	S. viridans	Light	6			
6	Right knee	.....	S. viridans	Light	1	+++	Prostate	5½
	Right knee	.....	S. viridans	Light	1			
	Left knee	.....	S. viridans	Light	2			
	Right ankle	.....	S. viridans	Light	2			
7	.....	Epitrochlear	S. viridans	Light	3	+++	Tonsils	15
	Left knee	.....	S. viridans	Light	3			
8	.....	Axillary	Gonococcus	Light	6	++	Prostate	⅔
	Left knee	.....	Gonococcus	Light	4			
	Left knee	.....	Gonococcus	Light	2			
	Left knee	.....	Gonococcus	Light	2			
	Left knee	.....	Gonococcus	Light	2			
	Left knee	.....	Gonococcus	Light	2			
9	Right knee	.....	S. viridans	Moderate	3	++++	Tonsils	1
		Right inguinal	S. viridans	Light	3			
10	Right knee	.....	Gonococcus	Light	2	++	Prostate	1
11	Right hip	.....	Staph. aureus	Moderate	2	++	Throat	2
12	Right hip	.....	S. viridans	Moderate	3	+	Throat	16
13	Right knee	.....	S. viridans	Light	3	++	Throat	1½
14	Left knee	.....	S. viridans	Light	1	+	Throat	12
15	.....	Right inguinal	S. viridans	Moderate	2	++	Throat	8
16	.....	Right inguinal	S. viridans	Light	3	++++	Sinus	6
17	.....	Epitrochlear	S. viridans	Light	3	+++	Sinus	1
18	.....	Right cervical	S. viridans	Moderate	3	++	Tonsils	3¼
19	.....	Left inguinal	S. viridans	Light	5	+	Throat	2½

centage of cases of chronic arthritis of nontuberculous and nonsyphilitic origin. It is also apparent that in the positive cases, repeated positive cultures can be obtained from the same or similarly involved joints. The coincidence of isolating the same organism from both the lymph nodes and the joints points toward these organisms as the etiologic agents in the arthritic cases reported.

CYTOLOGY OF SYNOVIAL FLUID

The data reported were accumulated from a study of thirty-three fluids from the knee joints of patients with chronic arthritis.

The literature contains but little work of real value on the histology of joint fluid. The textbooks of histology and pathology barely mention the subject. Abadie,[11] in 1902, examined the synovial fluid in three cases of chronic arthritis, termed by him "arthropathies tabétiques." He found the red blood cells always in great numbers, comprising from 60 to 80 per cent of the total cells present. Of the other elements, 87 per cent were small lymphocytes, 6 per cent were polymorphonuclears and 7 per cent "great mononuclears," endothelial cells and atypical cells. In two cases of arthritis deformans he found somewhat fewer cells, with 60 per cent red cells, 30 per cent lymphocytes and the remaining 10 per cent mononuclears and endothelial cells, without any polymorphonuclears.

Giffon and Abrami,[12] in 1907, described a fluid in a patient with syphilis. There was a polymorphonuclear preponderance which, after treatment, changed to a lymphocytic preponderance.

Singer,[13] in 1915, found joint fluid in arthritis associated with dysentery to be rich in polymorphonuclear leukocytes and lymphocytes.

Cecil,[14] in 1916, studied the pathology of joints and synovial fluid by injecting one or more doses of *Streptococcus viridans* into vitally stained rabbits. Acute or subacute infectious arthritis was produced in many cases. He stated that the joint sections showed a considerable number of large endothelial cells or macrophages in addition to numerous leukocytes. These macrophages, he believed, migrated from the tissue into the joint exudate and could not be seen to develop from the endothelial lining of the joint.

Labor and von Balogh,[15] in 1919, found cells in various arthritides as follows:

(*a*) Normal knee joint—from 10 to 20 cells per cubic millimeter; no wandering or endothelial cells.

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11. Abadie, M. J.: Examen cytologique du liquide articulaire de quelques arthropathies chroniques, Compt. rend. Soc. de biol., 1902, p. 945.

12. Giffon, V., and Abrami, P.: L'hydarthrose de la syphilis secondaire: Etude cytologique et expérimental de l'épanchment, cited in: Ann. d. mal. vén. **2:** 53, 1907.

13. Singer, G.: Erfahrungen aus der letzten Dysenterieepidemie, München. med. Wchnschr. **62:** 183, 1915.

14. Cecil, R. L.: A Study of Experimental Non-Hemolytic Streptococcus Lesions in Vitally Stained Rabbits, J. Exper. Med. **24:** 739, 1916.

15. Labor, M., and von Balogh, E.: Zytologische und serologische Untersuchungen der Synovia im besonderen bei akuten Gelenksentzündungen, Wien. klin. Wchnschr. **32:** 535, 1919.

(*b*) Acute rheumatism—always about 7,000 cells per cubic millimeter; mostly polymorphonuclear elements, with a few mononuclears, and about 3 per cent endothelial cells.

(*c*) Gonorrheal arthritis—about 16,000 cells per cubic millimeter; endothelial cells entirely absent in the acute stage.

(*d*) Rheumatoid dysentery—

(1) Acute stage—from 2,000 to 5,000 cells per cubic millimeter; polymorphonuclears more numerous than mononuclears; endothelial cells always present; but never more than from 2 to 3 per cent.

(2) Convalescent stage—from 750 to 1,500 cells per cubic millimeter; lymphocyte number may exceed the polymorphonuclears; endothelial cells increased to from 4 to 5 per cent.

Pewny,[16] in 1921, used the cell count of synovial fluid to distinguish between traumatic and tuberculous arthritis. He found that in tuberculous arthritis there were almost always a greater number of leukocytes (approximately 1,000) and fewer red cells than in traumatic arthritis. In the latter cases the white cells numbered from 400 to 600 cells per cubic millimeter.

Chesney, Kemp and Baetjer,[17] in 1926, made a careful study of ten patients all of whom had syphilis and arthritis. Five of these had definite syphilis of the joints. In three early cases they obtained total white cell counts of from 17,000 to 24,000 per cubic millimeter. In two late cases the counts were 2,480 and 1,500. In four of their cases of syphilis of the joints there were high percentages of lymphocytes and mononuclears combined (from 43 to 62 per cent). They did not separate the mononuclear elements.

The studies heretofore reported by various authors have been made from fixed films of the cells. Reports are not available on the character of the living cells in the synovial fluid. The supravital technic of studying living cells provides a means of obtaining more accurate and reliable data on their physiology and histology. By this means one can make observations on the ameboid activity, phagocytic power, behavior to altered environment, fragility, degenerative changes and other characteristics. Thus, information can be obtained concerning the life cycle of the cells.

The usual histologic methods require that the tissues should be subjected to rigorous measures, which not only obscure the physiologic processes of the cells, but also produce false pictures.

16. Pewny, W.: Cytologic Investigations of Tuberculous Effusions of Joints, Wien. klin. Wchnschr. **34:** 22, 1921.

17. Chesney, A. M.; Kemp, J. E., and Baetjer, F. H.: Experimental Study of Synovial Fluid of Patients with Arthritis and Syphilis, J. Clin. Investigation **3:** 131, 1926.

The behavior of blood cells toward vital dyes was studied by Rosin and Bibergeil in 1902 [18] and in 1904,[19] but it is the work of Evans and Scott,[20] Simpson [21] and Sabin [22] which has developed efficiently the so-called supravital technic. A brief description has been published by one of us (Forkner [23]) and is repeated here. For more detailed descriptions of the method, reference should be made to the works of the foregoing authors.

A thin film of dye in alcoholic solution is smeared across the surface of a previously cleaned, polished, and warmed glass slide. This is done by dipping the end of another slide, with which the smear is made on the former one into a fresh mixture (10 drops) of equal parts of 0.5 per cent alcoholic solution of neutral red, and a 0.1 per cent alcoholic solution of janus green. Solutions of the dyes are kept on hand, made up in 95 per cent alcohol. The dyes are not mixed until they are ready for use, because a mixture is not a stable preparation. Solutions of varying concentrations should be employed for making the dye films until one has gained proficiency in estimating the optimum concentration desired. Emphasis should be placed on staining the cells as lightly as is consistent to obtain good differentiation of the structures they contain. If the dyes are employed in concentrated solutions, the nuclei will be stained and the cells quickly killed. The glassware must be scrupulously clean, because cells are delicate structures, and any acid, alkali, or the like will injure their membranes, and markedly alter their physiologic behavior.

Janus green and neutral red are relatively nontoxic dyes. The former in dilute concentration is a specific stain for mitochondria, and the latter a specific stain for cytoplasmic structures.

In the study of living blood cells, a freely flowing drop of blood is obtained on the under surface of a coverslip, and allowed to fall gently on the slide prepared with the dye. With blood, the plasma takes up some of the dye, and the cells are bathed in the dilute solution from which they become specifically stained. The same procedure is easily applicable to joint fluid.

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18. Rosin, H., and Bibergeil, E.: Ergebnisse vitaler Blutfärbung, Deutsche med. Wchnschr. **27:** 41, 1902.

19. Rosin, H., and Bibergeil, E.: Das Verhalten der Leucocytes bei den vitalen Blutfärbung, Virchows Arch. f. path. Anat. **178:** 478, 1904.

20. Evans, H. M., and Scott, K. T.: On the Segregation of Macrophage and Fibroblast Cells by Means of Vital Acid Dyes and on the Cause of the Differential Effect of These Substances, Anat. Record **16:** 148, 1919.

21. Simpson, M. E.: Vital Staining of Human Blood with Special Reference to the Separation of Monocytes, Univ. California Pub. Anat. **1:** 1, 1921.

22. Sabin, F. R.: Studies on Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34:** 277, 1923.

23. Forkner, C. E.: Material from Lymph Nodes of Man: Method to Obtain Material by Puncture of Lymph Nodes for Study with Supravital and Fixed Stains, Arch. Int. Med. **40:**532 (Oct.) 1927.

Normal joint fluid is clear, thick and stringy. Pathologic states in which there is an increase in joint fluid and increased cellular content show a decreased viscosity and various degrees of turbidity and yellowish color. Because of these characteristics, the joint fluid, when diluted with acetic acid solution, as in the making of ordinary white blood cell counts, forms a heavy cloud in the pipet, preventing accurate enumeration of the cellular elements. For this reason, the fluid is counted either without dilution, or by dilution with physiologic sodium chloride solution. An ordinary blood counting chamber may be used. Total and differential counts were made in all instances.

The cellular content of the normal and pathologic synovial fluid consists of blood cells and certain tissue cells. Red blood cells are not found in normal fluid, and are rarely present in chronic, nontuberculous, nonsyphilitic arthritis, except as the result of trauma. All types of white blood cells may be found. Occasional clasmatocytes (macrophages) and synovial mesothelial cells may be seen. The term "mesothelial cell" is used to designate the lining cell of the synovial membrane. It is comparable to the endothelial or epithelial cell of other authors. Table 4 gives, at a glance, the essential characteristics of such cells, when stained by the supravital method with neutral red and janus green.

Table 5 gives the cell counts in the joint fluids of patients with chronic arthritis in which bacterial cultures were positive.

Table 6 gives the cell counts in three cases in which regional lymph node cultures were positive, but in which joint fluids were negative.

Table 7 gives the cell count of the synovial fluid in cases in which both the joint fluid and the lymph nodes were bacteriologically negative.

Table 8 gives the cell count in cases in which the joint fluid was negative and the lymph nodes were not cultured.

The average of all the positive joint fluids is as follows: total white cell count, 11,018, percentage of neutrophils, 61.2; basophils, 0.22; eosinophils, 0.1; monocytes, 15.1; lymphocytes, 19.1; clasmatocytes, 3.22; unclassified, 0.9. On the other hand, the average of all the negative joint fluids is as follows: total white cell count, 5,670; percentage of neutrophils, 50.1; basophils, 0.29; eosinophils, 0.17; monocytes, 19.78; lymphocytes, 26.28; clasmatocytes, 2.59; mesothelial cells, 0.61; unclassified, 0.05.

COMMENT

Study of the tables reveals several interesting observations. 1. Both the highest and lowest total number of cells were encountered in the joint fluids from which positive cultures were obtained. 2. The synovial fluids in all the cases studied invariably had an increased white cell count. 3 The average total white cell count of the bacteriologically

TABLE 4.—*Description of Living Cells Found in Synovial Fluid, Stained with Neutral Red and Janus Green*

	Polymorphonuclear Neutrophils	Polymorphonuclear Basophils	Polymorphonuclear Eosinophils	Monocytes	Lymphocytes	Macrophages	Mesothelial Cells
Size	Approximately 16 to 20 microns	Approximately 16 to 20 microns	Approximately 16 to 20 microns	Approximately 10 to 22 microns	Approximately 5 to 20 microns	Approximately 12 to 35 microns	Approximately 10 to 30 microns
Motility	Active; streaming of granules; nucleus in rear of cell; some nonmotile cells	Slightly active; same type as neutrophil	Active; same type as neutrophil	Moderately active; nucleus remains near center of cell	Moderately active; nucleus in front of cell	Slightly active; nucleus remains near center of cell	Not motile; cells are probably degenerating
Phagocytosis	Occasionally contain ingested material	Rarely phagocytic	Rarely phagocytic	Phagocytic	Little phagocytosis	Marked phagocytosis	Moderately phagocytic
Nucleus	Polymorphonuclear	Polymorphonuclear	Polymorphonuclear	Round, indented, kidney or horseshoe shape	Round, oval or indented	Round or oval	Round or oval
Cytoplasm	Well filled with specific granules	Well filled with specific granules	Well filled with specific granules	Gray, appearance like ground glass, containing vacuoles and mitochondria	Clear, hyaline, containing from 1 to 10 vacuoles and numerous mitochondria	Filled with débris and ingested cells	May have few refractive neutral red bodies; cytoplasm has grayish granular appearance
Specific granules	Bright, refractive, and only slightly stained; yellowish tinge	Deep red; slightly less refractive than neutrophil granules; even in size	Large, refractive, copper-yellow granules; not always perfectly round	None	None	None	None
Segregation bodies or vacuoles* (red, brown, yellow)	From 0 to 10 red bodies among the bright refractive, specific granules of the cytoplasm	Occasional red vacuole	Vacuoles not so evident owing to nature of specific granules	From 25 to innumerable red-brown, nonrefractive bodies, with occasional larger brown refractive body; uneven in size; may be clustered around centrosphere or scattered through cytoplasm	From 1 to 10 refractive bodies of various sizes, often redder and more refractive than those of monocyte	Many bodies of all sizes and shapes, varying from yellow to red	Occasional refractive, reddish body
Mitochondria (blue to green)	Occasionally seen in clear area of cytoplasm as delicate rods or filaments	Difficult to demonstrate	Occasionally seen in clear area of cytoplasm as delicate rods or filaments	Numerous; usually small in size; often scattered through cytoplasm; delicate dots, rods or filaments	Numerous; usually perinuclear; usually large; rods, dots or filaments	Difficult to demonstrate; may be shown by staining with Janus green alone	Do not stain

* The term "segregation bodies," or "vacuoles," is used in this paper to designate those structures of the cytoplasm which have the property of segregating the dye and concentrating it in vacuoles. These vacuoles often increase in size with longer exposure to the dye.

TABLE 5.—*Cytology of Synovial Fluid from Which Bacteria Were Grown*

Case	Total White Cell Count per C.Mm.	Percentage of Polymorphonuclears			Percentage of					Total Number per C.Mm. Polymorphonuclears			Total Monocytes	Total Lymphocytes	Total Clasmatocytes	Total Mesothelial Cells	Total Unclassified Cells	Clinical Activity of Joint
		Neutrophils	Basophils	Eosinophils	Monocytes	Lymphocytes	Clasmatocytes	Mesothelial Cells	Unclassified Cells	Neutrophils	Basophils	Eosinophils						
5	39,500	89	..	1	4	6	..	..	..	35,155	...	395	1,580	2,370	.....	..	..	+++
4	23,680	93	..	..	1	4	2	..	..	22,022	...	...	237	947	474	..	..	++++
7	15,680	42	..	..	3	48	7	..	..	6,586	...	...	470	7,526	1,098	..	..	+++
	13,000	49	..	..	13	27	11	..	..	6,370	...	...	1,690	3,510	1,430	..	..	+++
8	3,240	87	..	..	8	5	..	..	..	2,819	...	...	259	162	.....	..	..	++
6	3,000	94	..	..	3	2	1	..	..	2,820	...	...	90	60	30	..	..	+++
9	900	70	..	..	8	8	4	..	8	630	...	...	72	72	36	..	72	++++
2	80	10	..	..	40	50	..	..	..	8	...	...	32	40	.....	..	..	+++
14	80	17	2	..	56	22	4	..	..	14	1.6	...	45	18	3	..	..	+
Aver.	11,018	61.2	0.22	0.11	15.1	19.1	3.22		0.9									

TABLE 6.—*Cytology of Synovial Fluid from Cases in Which Regional Lymph Nodes Were Bacteriologically Positive but Synovial Fluid Was Sterile*

Case	Total White Cell Count per C.Mm.	Percentage of Polymorphonuclears			Percentage of					Total Number per C.Mm. Polymorphonuclears			Total Monocytes	Total Lymphocytes	Total Clasmatocytes	Total Mesothelial Cells	Total Unclassified Cells	Clinical Activity of Joint
		Neutrophils	Basophils	Eosinophils	Monocytes	Lymphocytes	Clasmatocytes	Mesothelial Cells	Unclassified Cells	Neutrophils	Basophils	Eosinophils						
17	5,720	57	..	..	24	17.8	1.2	..	..	3,260	...	...	1,373	1,018	69	..	..	+++
18	600	34	..	..	18	44	3	..	..	204	...	...	108	264	18	..	..	++
19	500	82.8	..	..	8.6	8.6	...	..	..	414	...	...	43	43	..	..	..	+
Aver.	2,273	57.9			16.9	23.5	1.4											

TABLE 7.—*Cytology of Synovial Fluid of Cases in Which Regional Lymph Nodes and Joint Fluid Were Both Sterile*

Case	Total White Cell Count per C.Mm.	Percentage of Polymorphonuclears			Percentage of					Total Number per C.Mm. Polymorphonuclears			Total Mono-cytes	Total Lym-pho-cytes	Total Clas-mato-cytes	Total Meso-thelial Cells	Total Unclas-sified Cells	Clinical Activity of Joint
		Neutro-phils	Baso-phils	Eosino-phils	Mono-cytes	Lym-pho-cytes	Clas-mato-cytes	Meso-thelial Cells	Unclas-sified Cells	Neutro-phils	Baso-phils	Eosino-phils						
20	18,400	82	..	..	9	7	2	..	..	15,088	...	...	1,656	1,288	368	..	..	++++
	15,040	63	..	..	13	20	4	..	..	9,475	...	...	1,955	3,008	602	..	..	++
	11,360	58	..	..	10	28	3	1	..	6,589	...	...	1,136	3,181	341	114	..	++
21	10,240	67	..	..	22	11	..	..	..	6,861	...	...	2,253	1,126	...	..	..	+++
22	1,200	28	..	..	22	46	4	..	..	336	...	...	264	552	48	..	..	++
23	2,080	80	..	..	3	16	1	..	..	1,664	...	...	62	333	21	..	..	++
Aver.	9,720	63			13.3	21.3	2.3	0.17										

TABLE 8.—*Cytology of Synovial Fluid in Which Fluid Was Sterile and Lymph Nodes Were Not Cultured*

Case	Total White Cell Count per C.Mm.	Percentage of Polymorphonuclears			Percentage of					Total Number per C.Mm. Polymorphonuclears			Total Mono-cytes	Total Lym-pho-cytes	Total Clas-mato-cytes	Total Meso-thelial Cells	Total Unclas-sified Cells	Clinical Activity of Joint
		Neutro-phils	Baso-phils	Eosino-phils	Mono-cytes	Lym-pho-cytes	Clas-mato-cytes	Meso-thelial Cells	Unclas-sified Cells	Neutro-phils	Baso-phils	Eosino-phils						
24	25,920	95	..	..	5	..	..	..	..	24,624	..	...	1,296	.....	...	..	..	++++
25	16,480	88	..	..	5	4	3	..	..	14,502	..	...	824	659	494	..	..	++++
26	9,440	89	1	..	7	2	1	..	..	8,402	94	...	661	189	94	..	..	+
27	7,840	85	..	..	7	6	..	..	..	6,664	..	...	549	470	..	..	..	++
28	2,950	84	..	..	10	5	1	..	..	2,478	..	...	295	148	29	..	..	++
29	2,720	27.5	..	..	6.9	64.4	..	..	1.2	748	..	...	188	1,752	..	..	33	+
30	2,125	63.4	1.3	..	24	8.8	2.5	..	..	1,347	28	...	510	187	53	..	..	+++
31	1,800	20	..	..	20	60	..	..	..	360	..	...	360	1,080	..	..	..	+
32	400	14.7	..	..	34.3	42	..	9	..	59	..	...	137	168	..	36	..	++
33	350	..	..	..	50	50	..	..	..	..	..	...	175	175	..	..	..	+
34	300	12	..	..	44	44	..	..	..	36	..	...	132	132	..	..	..	+
35	300	10	..	..	65	25	..	..	..	30	..	...	195	75	..	..	..	++
36	110	12	4	4	40	28	8	4	..	13	4.4	4.4	44	31	8.8	4.4	..	+++
37	100	..	..	..	7	67	26	..	..	..	..	...	7	67	26	..	..	+
38	100	..	..	..	..	..	..	..	..	..	..	...	..	..	..	..	..	+
Aver.	4,729	42.9	0.45	0.29	23.2	29	3	0.92	0.08									

positive joint fluids was approximately double that of the negative joint fluids. 4. The highest total white cell counts and the highest incidence of positive cultures were found, as a rule, in the fluids of the most clinically active joints. There were exceptions to this rule. 5. The polymorphonuclear neutrophils were 11.1 per cent higher in the group of positive joints than in the negative joints. The clasmatocytes were likewise increased in this group. The number of monocytes and lymphocytes was definitely higher in the negative joint fluids than in the positive fluids. 6. Desquamated mesothelial cells are by no means a constant observation in the arthritic joint fluid. When encountered they appear to be degenerating cells, as will be seen in table 4. 7. The average percentage of mononuclear cells in the joint fluids of patients with chronic nonsyphilitic and nontuberculous arthritis is approximately the same as that recorded by Chesney, Kemp and Baetjer [17] in patients with syphilitic joint disease.

X-ray studies were made in this group of cases, but new information could not be reported. A definite relationship did not exist between the x-ray changes and the cytologic evidence. The number and types of cells found cannot be foretold by study of the roentgenograms. Brief x-ray reports are recorded with the case histories.

SUMMARY

1. Bacteriologic and cytologic studies of the synovial fluids in sixty-three cases of chronic, nonsyphilitic and nontuberculous arthritis are reported. The results of lymph node cultures in twenty-one of these cases are recorded.

2. Positive cultures were obtained from the joint fluid in 22 per cent of the total number of cases. Positive growths were obtained in 48 per cent of the lymph nodes cultured.

3. Increased white cell counts in the synovial fluid were found in all cases. The average white cell count in the synovial fluid in the bacteriologically positive cases was approximately double that in the negative cases. The number of polymorphonuclear neutrophils was distinctly higher in the group in which positive cultures were obtained in the joint fluid. The number of monocytes and lymphocytes was definitely higher in the group in which negative cultures were obtained in the joint fluid. Synovial mesothelial cells are not a constant observation in arthritic joint fluid.

4. Case reports are given of patients with positive bacteriologic cultures of synovial fluid and lymph nodes.

REPORT OF CASES

CASE 1.—*History.*—Miss A. B., aged 52, was seen in the dispensary on March 11, 1927, with the complaint of pain, swelling and stiffness of the knee joints. A diagnosis was made of chronic infectious arthritis. The onset of pain in the

knees, especially the left, had been gradual, having begun two years before. The knees were swollen and stiff, and grating was noted. No other joints were involved.

The patient's health was excellent in general up to that time. Infected teeth were removed one year after the onset. Sore throat and colds occurred frequently. She suffered from chronic constipation. An appendectomy had been performed in 1916. Nocturia had occurred once a night for many years.

Examination.—The patient was obese. The blood pressure was 190 systolic and 160 diastolic. The lymph nodes were not enlarged. The tonsils were small, pale and scarred; nothing could be expressed from the crypts. Many teeth were missing; abscesses were not found. The sinuses were clear. The heart and lungs were normal. The abdomen was normal. The joints of the knees showed tenderness, swelling and crepitus. Observations in the pelvis were negative.

Laboratory examinations revealed the following results: The Wassermann reaction was negative. The urine was normal, except for a trace of sugar. X-ray pictures of the left knee showed hypertrophic arthritis. Aspiration was performed on the left knee on March 24, 1927; a few drops of cloudy fluid were removed. Culture showed a light growth of *Streptococcus viridans.* Sufficient fluid for a cell count was not obtained.

CASE 2.—*History.*—L. B., a widow, aged 47, was admitted on Jan. 20, 1927, with the complaint of pain, stiffness and swelling of the joints. A diagnosis was made of chronic infectious arthritis of the right knee, hands and spine. She had had recurrent pain and stiffness in the right knee and in the fingers for about seven years. The patient was admitted to the hospital because of abdominal pain due to a properitoneal hernia for which operation was performed. While she was recuperating from the operation, an exacerbation of the arthritis occurred, with pain, stiffness and swelling of the right knee and the hands.

The patient's health had been poor in general. She had had diphtheria, typhoid fever, scarlet fever, malaria, measles and mumps. The appendix had been removed and the gallbladder drained twenty-three years before. Headaches and stiff neck were of frequent occurrence. Sore throat occurred occasionally. She had had pneumonia, pleurisy and influenza. Nocturia had been present for eight years, causing urination from three to five times each night.

Examination.—The patient was obese. The blood pressure was 194 systolic and 96 diastolic. Enlargement of the lymph nodes was not observed. The tonsils were moderately enlarged and reddened. Several teeth were missing; a considerable amount of dentistry had been performed. The heart was moderately enlarged; the aortic second sound was accentuated, the peripheral vessels were moderately sclerosed. The lungs were clear. The abdomen was normal, except for a properitoneal hernia. The pelvis contained small hard Bartholin's glands, but was otherwise normal. The right knee showed tenderness, swelling and crepitus; the hands were slightly swollen and stiff; the lumbar spine was slightly tender, and motion was restricted.

Laboratory examination of the blood revealed: red cells, 4,944,000; hemoglobin content, 83 per cent (Sahli); white cells, 11,100; polymorphonuclears 66 per cent. The Wassermann reaction was negative. The urine gave negative observations except for faint trace of albumin. An x-ray picture (fig. 1) of the right knee showed infectious arthritis. The exostoses on the tibial spines and on the inner aspects of the femoral condyles should be noted in figure 1. There was an irregularity about the external condyle of the tibia, and a moder-

ate amount of bone atrophy. By aspiration of the right knee on May 5, 1927, a few cubic centimeters of normal fluid were obtained. Culture showed a light growth of *S. viridans*. The cell count was 80 per cubic millimeter. The differential count showed: neutrophils, 10 per cent; lymphocytes, 50 per cent; and monocytes, 40 per cent.

The patient was discharged on May 6, 1927.

CASE 3.—*History.*—E. B., a man, aged 37, married, was seen in the dispensary on March 16, 1927, with a complaint of soreness and tenderness of the wrists

Fig. 1 (case 2).—Infectious arthritis of the right knee. The exostoses on the tibial spines and on the inner aspects of the femoral condyles should be noted. Irregularity is seen about the external condyle of the tibia, and there is a moderate amount of bone atrophy.

fingers, knees, ankles and back. A diagnosis was made of chronic infectious arthritis. Two months previously, the patient had an attack of quinsy and tonsillitis. Five weeks later, the wrists, elbows, knees and ankles became painful and swollen; this condition persisted. The most marked symptoms were in the left knee.

The patient's health had been excellent in general. He had sore throat frequently as a child, and cold with a cough occasionally. A gonorrheal infection was present fifteen years before.

Examination.—The patient was well nourished and developed. There was a slight enlargement of the lymph nodes. The tonsils were enlarged and showed evidence of chronic infection; there was hypertrophy of the lymphoid tissue in the posterior pharynx. Several teeth were missing; the others were in poor condition; two periapical rarefactions were noted. The heart and lungs were normal. The observations in the abdomen were negative. Enlargement and tenderness were not noted in the prostate. The joints of the fingers were quite sensitive and showed Haygarth's nodes; there was some swelling and tenderness of the wrists; the knees showed slight swelling and tenderness, with evidence of an increase of fluid; the left ankle was extremely swollen and tender, with limitation of motion; the spine was tender in the lumbar region with restriction of motion.

Laboratory examinations revealed the following: X-ray pictures of the left knee showed periarticular swelling. By aspiration of the left knee on March 17, 1927, 3 cc. of thick syrupy fluid was obtained. Culture showed a light growth of *S. viridans.* A total cell count was not made because of the scarcity of cells. The differential count revealed: neutrophils, 32 per cent; lymphocytes, 18 per cent, and monocytes, 50 per cent.

CASE 4.—*History.*—Mrs. E. F., aged 48, was admitted on July 20, 1927, with the complaint of soreness, stiffness and swelling of the wrists, fingers, shoulders, knees and ankles. A diagnosis was made of chronic infectious arthritis. Swelling and soreness in the ankles was first noted ten years previously; six months later it appeared in the arms and wrists, and still later through her shoulders and knees. This condition became progressively worse.

The patient's health was good in general until that time. Nine years before admission to the hospital a nasal operation was performed; seven years before admission the tonsils were removed. Corneal ulcers occured about every two years. Constipation was marked. There had been three pregnancies and one miscarriage. A leukorrheal discharge was observed for several years. The patient had lost 16 pounds (7.3 Kg.) during the last year.

Examination.—The patient was markedly undernourished and in considerable pain. There was a moderate enlargement of the lymph nodes. The tonsils had been cleanly removed. The sinuses were clear. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal, except for slight tenderness in the right upper quadrant. The pelvis revealed marked laceration of the cervix with chronic cervicitis. There was marked swelling of the wrists with deformities of the hands and fingers; the elbows, shoulders, knees and ankles were swollen and tender with limitation of motion; the knees showed evidence of an increase of fluid.

Laboratory examination of the blood revealed: red cells, 4,110,000; hemoglobin content, 70 per cent (Sahli); white cells, 9,400; polymorphonuclears, 68 per cent; lymphocytes, 30 per cent, and monocytes, 2 per cent. The Wassermann reactions in the blood and spinal fluid were negative. The urine gave negative observations, except for slight trace of albumin. The x-ray picture of the right knee (fig. 2) showed marked infectious arthritis. Marked narrowing of the joint space, atrophy of the bone, irregularity of the external condyle of the femur and the exostoses on the internal condyles of the femur and tibia should be noted in figure 2. Culture of the lymph nodes of the right inguinal group on July 21, 1927 revealed a moderate growth of *S. viridans.* Aspiration of the right knee on July 21, 1927, produced a large amount of turbid fluid. Culture showed *S. viridans.* The cell count was 23,680 per cubic millimeter. The differ-

ential count revealed: neutrophils, 93 per cent; lymphocytes, 4 per cent; monocytes, 1 per cent, and macrophages, 2 per cent. Many vacuolated cells were present; the neutrophils were very active.

The patient was discharged on Aug. 17, 1927.

CASE 5.—*History.*—H. F., a man, aged 40, married, was seen in the dispensary on May 24, 1927, with a complaint of swelling, pain and stiffness in the ankles, knees, hips, hands and neck. A diagnosis was made of multiple infectious arthritis. The onset had been gradual eighteen months previously, with pain

Fig. 2 (case 4).—Infectious arthritis of the right knee. The knee shows marked involvement. The narrowing of the joint space, atrophy of the bones, irregularity of external condyle of femur and the exostoses on the internal condyles of the femur and tibia should be noted.

in the right hip and knee. At this time, some pain was noted in the right hand with swelling, which became progressively worse. Ten months before admission to the dispensary, further extension occurred to the other joints mentioned.

The patient's health had been excellent. He had sore throat occasionally. All the teeth were out. His appetite was good, and bowel movements were regular. He had not had any venereal disease.

Examination.—The patient was poorly nourished. There was a moderate enlargement of the lymph nodes. The tonsils were small, adherent and not

inflamed. The sinuses were clear. The teeth had all been extracted. The heart and lungs were normal. The edge of the liver was just palpable. The prostate was normal. The wrists, fingers, elbows, shoulders and knees all showed tenderness with limitation of motion; there was an increase of fluid in the knees; the hands showed atrophic changes.

Laboratory examinations revealed the following results: The urine was normal. The Wassermann reaction was negative. An x-ray picture of the right knee showed periarticular swelling. Culture of a lymph node excised from the left epitrochlear showed a light growth of *S. viridans*. Aspiration of the right knee on June 2, 1927, yielded 50 cc. of turbid, straw colored fluid. Culture showed a growth of *S. viridans*. The cell count was 41,920. The differential count revealed: neutrophils, 82 per cent; lymphocytes, 11 per cent, and monocytes, 7 per cent. Aspiration of the right knee on July 30, 1927, yielded the same type and quantity of fluid as was obtained previously. Culture showed *S. viridans*. The cell count was 39,500. The differential count revealed: neutrophils, 89 per cent; eosinophils, 1 per cent; lymphocytes, 6 per cent, and monocytes, 4 per cent.

Case 6.—*History.*—J. G., a man, aged 40, unmarried, was admitted Jan. 29, 1927, with the complaint of pain in the back, stiffness in the muscles and neck and soreness all over. A diagnosis of chronic infectious arthritis was made. The onset occurred about five and one-half years before, with pain in the right hip, the back of the thigh and the right knee. This pain was characterized by attacks coming on every few weeks lasting two or three days. Four years before admission to the hospital, the stiffness and soreness in the back increased. Two and one-half years before admission, he had considerable palpitation and noticed some irregularity of the heart. Thirteen months before admission, a tonsillectomy was done and four abscessed teeth were extracted; this was followed by a prompt clearing up of the arthritis. One year before admission, he noticed that his right sternoclavicular joint was enlarged. During the eight months before admission, many joints were involved but especially those of the dorsal and cervical vertebrae.

The patient's health was fair previously. He had scarlet fever, measles and pneumonia as a child. He had rheumatic fever at the age of 23, and also at 19. Eight years before, he had tonsillitis and quinsy, and during this attack he noticed that his joints were inflamed, particularly in the upper extremities. Nine years before, he had influenza and pneumonia. Constipation of a moderate degree had been present. He had gonorrhea at the ages of 19, 20 and 23. He had lost 20 pounds (9 Kg.) during the last year.

Examination.—The patient was emaciated and apprehensive. There were a few palpable lymph nodes in the groins, but no general glandular enlargement. A few tonsillar tags remained; culture from throat showed a beta-hemolytic streptococcus. Several teeth had been removed; the remaining teeth were in fair condition. The blood pressure was 112 systolic, and 62 diastolic. There was moderate enlargement of the heart to the left with a systolic murmur at the apex. The lungs were clear. The abdomen was normal. The right lobe of the prostate was moderately enlarged and somewhat thickened, but not tender; the left lobe was slightly enlarged. The spine showed considerable stiffness and tenderness; the knees and ankles showed moderate swelling and tenderness, with limitation of motion; the right shoulder showed tenderness, swelling, and limitation of motion; the right sternoclavicular joint was swollen and sore.

Laboratory examinations of the blood revealed: red cells, 4,000,000; hemoglobin content, 72 per cent (Sahli); white cells, 10,320, and polymorphonuclears,

70 per cent. The Wassermann reaction was negative. The urine was clear. X-ray pictures of the lumbar spine showed infectious arthritis. The right inguinal node was excised and did not show any growth on culture mediums on Feb. 9, 1927. A few days after this, there was an acute exacerbation with involvement of almost all the joints, particularly the knees, with marked swelling, redness, pain and stiffness. Culture of the blood during this time was positive for *S. viridans* on one examination. By aspiration of the right knee and ankle on Feb. 28, 1927, about 35 cc. of cloudy, straw colored fluid was obtained from the knee, and about 5 cc. from the ankle. Cultures from both fluids showed *S. viridans*. The cell count was 3,000. The differential count revealed: neutrophils, 94 per cent; lymphocytes, 2 per cent; monocytes, 3 per cent, and macrophages, 1 per cent. Aspiration of the right knee on March 3, 1927, yielded the same results as were obtained previously. Aspiration was performed on the right knee on March 10 and 14, 1927; the culture was negative. Aspiration was performed on the right knee on May 18, 1927; the culture showed *S. viridans*.

The patient was discharged on May 20, 1927.

CASE 7.—*History.*—C. K., a man, aged 42, married, was admitted on April 29, 1927, with a complaint of soreness, swelling and stiffness of the joints of the arms and legs, especally in the knees and hands. A diagnosis was made of chronic infectious arthritis. The onset had been gradual over a period of fifteen years, starting in the fingers of the right hand and spreading to the right wrist and ankles. Two and one-half years before admission to the hospital, the back, and then the feet, elbows, shoulders and knees became involved. Associated with the pains in the joints he had noticed a loss of weight and appetite with a decrease of strength.

His health had been fair. He had measles, mumps with orchitis, influenza twice and malaria. He had otitis media with drainage at the age of 20. An infection of the sinuses occurred at 16. Tonsillitis and abscessed teeth were not noted. Constipation with bilious attacks was frequent. Venereal infection had not occurred. Nocturia causing urination one or two times each night was present for two years. There was occasional pain with micturition.

Examination.—The patient was rather poorly nourished, with considerable deformity and crippling. The blood pressure was 138 systolic and 88 diastolic. Marked enlargement of the lymph nodes was noted. The tonsils were small, scarred and embedded, but did not appear to be infected. The sinuses were clear. The teeth appeared to be in fair condition. The heart and lungs were normal. The abdomen was normal. The prostate was slightly enlarged, soft and uniform, and not tender. The feet, knees, shoulders, elbows and hands showed swelling, tenderness, crepitus and limitation of motion; the spine was stiff and showed some limitation of motion; the hands showed atrophic changes.

Laboratory examinations of the blood revealed: red cells, 4,800,000; hemoglobin content, 84 per cent (Sahli); white cells, 6,550, and polymorphonuclears, 69 per cent. The Wassermann reaction was negative. The urine was normal. An x-ray picture of the right hand showed marked infectious arthritis. A culture was made of the right inguinal lymph node on April 29, 1927. The growth showed *S. viridans*. Aspiration of the right knee on April 29, 1927, yielded 50 cc. of turbid, straw colored fluid, which gave a positive growth of *S. viridans*. The cell count was 13,000. The differential count was neutrophils, 49 per cent; lymphocytes, 27 per cent; monocytes, 13 per cent, and macrophages, 11 per cent. Aspiration of the right knee on May 3, 1927, yielded the same amount of fluid

as was obtained previously, showing *S. viridans*. The cell count was 15,680. The differential count was: neutrophils, 42 per cent; lymphocytes, 48 per cent; monocytes, 3 per cent, and macrophages, 7 per cent.

CASE 8.—*History.*—P. L., a man, aged 51, married, was admitted on Dec. 15, 1926, with a complaint of pain and swelling of the joints, especially the knees, shoulders and hands. A diagnosis was made of chronic infectious arthritis. The onset had been rather abrupt eight months before with pain through the arches of the feet. After two months, this spread to the left knee, left hip, left hand and practically all the joints. Three months before admission to the hospital, the right jaw became affected. There was considerable pain, swelling and stiffness in the joints.

The patient's health was fair up to that time. He had severe headaches frequently. All the teeth had been out for eighteen years. Bowel movements were fairly regular, and indigestion was not noted. Eight years before admission, he had a gonorrheal infection which subsided, and then he was reinfected. At that time he had a sore heel for a few days which entirely cleared up. He suffered from constipation for fifteen years. Nervous breakdowns occurred fifteen years and one year before admission. He lost 28 pounds (12.7 Kg.) during the last six months.

Examination.—The patient was somewhat undernourished and had an extremely nervous temperament. There was moderate enlargement of the lymph nodes. The tonsils were scarred, embedded and red, and showed a few whitish areas, indicating a chronic tonsillar infection. Culture revealed a beta-hemolytic streptococcus. An old infection was observed in the left antrum. The x-ray picture was reported to be clear. The teeth had all been extracted. The heart and lungs were normal. The abdomen was normal. The prostate was slightly enlarged with more pus cells than normal. The knees, ankles and hands were swollen and tender, had a limitation of motion and showed crepitus; the hips, elbows and shoulders showed tenderness, crepitus and limitation of motion.

Laboratory examination of the blood revealed: red cells, 3,400,000; hemoglobin content, 75 per cent (Sahli); white cells, 7,800, and polymorphonuclears, 72 per cent. The Wassermann reaction was negative. The urine was normal. X-ray pictures of the left foot showed slight infectious arthritis. The lymph node in the left axilla was punctured on Jan. 8, 1927. The culture was positive for gonococci. The material withdrawn showed an increased number of neutrophils in the node. Aspiration of the left knee on Jan. 14, 1927, yielded a small amount of yellow fluid. The culture was positive for gonococci. The cell count was 3,240 per cubic millimeter. The differential count was: neutrophils, 87 per cent; lymphocytes, 5 per cent, and monocytes, 8 per cent. Aspiration was performed on the left knee on Feb. 23, March 10 and March 27; gonococci were again recovered in culture.

CASE 9.—*History.*—Mrs. G. M., aged 32, was admitted on March 24, 1927, with the complaint of swollen, tender and painful joints. A diagnosis was made of chronic infectious arthritis. The onset had been sudden one year before, with swelling and tenderness in the right knee. The swelling lasted a few days, and then had a tendency to recur repeatedly. Six months later, the left elbow became involved. Three months before admission to the hospital, the toes and knee on the left side were affected, followed by involvement of the right ankle and the left elbow. Recently, the wrists became involved, and in the last two weeks, the jaws and neck.

The patient's health had been excellent. There were many fillings in the teeth. Some constipation was present recently.

Examination.—The patient was poorly nourished. Moderate enlargement of the lymph nodes was observed. The tonsils were small and not injected, but they showed a chronic infection. The sinuses were clear. The teeth showed several crowns and one periapical infection. The heart and lungs were normal. The abdomen was normal. The pelvis was free from infection. The knees and ankles showed swelling, tenderness, crepitus, limitation of motion and fluid; the elbows and hands showed swelling, tenderness and limitation of motion; the cervical spine and jaws showed tenderness and limitation of motion.

Laboratory examination of the blood revealed: white cells, 8,320; hemoglobin content, 52 per cent (Sahli). A Wassermann test was not done. The urine was normal. An x-ray picture of the right knee showed infectious arthritis. Culture of the right inguinal node excised on March 31, 1927, showed a light growth of *S. viridans.* Aspiration of the right knee on March 31, 1927, yielded a fair amount of slightly turbid, straw colored fluid. The culture showed a moderate growth of *S. viridans.* The cell count was 900 per cubic millimeter. The differential count was: neutrophils, 70 per cent; lymphocytes, 8 per cent; monocytes, 8 per cent; macrophages, 4 per cent; degenerating cells, 6 per cent, and unclassified, 2 per cent.

The patient was discharged on April 5, 1927.

CASE 10.—*History.*—E. M., an unmarried man, aged 22, was seen in the dispensary on Feb. 14, 1927, with a complaint of swelling and stiffness of the right knee. A diagnosis was made of chronic synovitis of the right knee. The onset of the condition occurred one year before with pain and swelling of the right knee, associated with slight pain in the left ankle and right thigh. The pain and swelling of the knee persisted. At this time the patient had an acute urethritis.

The patient's health had been excellent. He had an occasional sore throat, and there were a few bad teeth.

Examination.—The patient was well nourished and well developed. There was no enlargement of the lymph nodes. The tonsils were enlarged and infected. The teeth showed some devitalization. Epididymitis was present, with chronic tenderness of the ankles.

Laboratory examinations revealed the following results: the Wassermann reaction was negative. X-ray pictures of the right knee showed the bones to be normal, and an increase in fluid. Aspiration of the right knee on Feb. 15, 1927, yielded a large amount of turbid, yellow fluid. Culture showed a positive growth of gonococci.

CASE 11.—*History.*—Mrs. A. N., aged 46, was admitted June 12, 1927, with a complaint of pain and stiffness in the right hip and leg. A diagnosis was made of hypertrophic arthritis of the right hip. The onset occurred two years before at the time of a fall on the right hip which was followed by pain and stiffness in the joint. This became progressively worse, the pain now radiating down the leg. At times the pain became so severe that the patient fell down. Slight pain and stiffness was noted through the left little finger.

The patient's health was excellent. She had sore throat and catarrh occasionally. She suffered from chronic constipation.

Examination.—The patient was well nourished. There was no enlargement of the lymph nodes. The tonsils were normal. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal. The pel-

vis was normal. Pain was elicited in the right hip on manipulation, with a limitation of all motion, especially flexion and external rotation.

Laboratory examinations revealed the following results: The Wassermann reaction was negative. The urine was normal. An x-ray picture (fig. 3) of the right hip showed hypertrophic arthritis. The marked proliferation of the bone

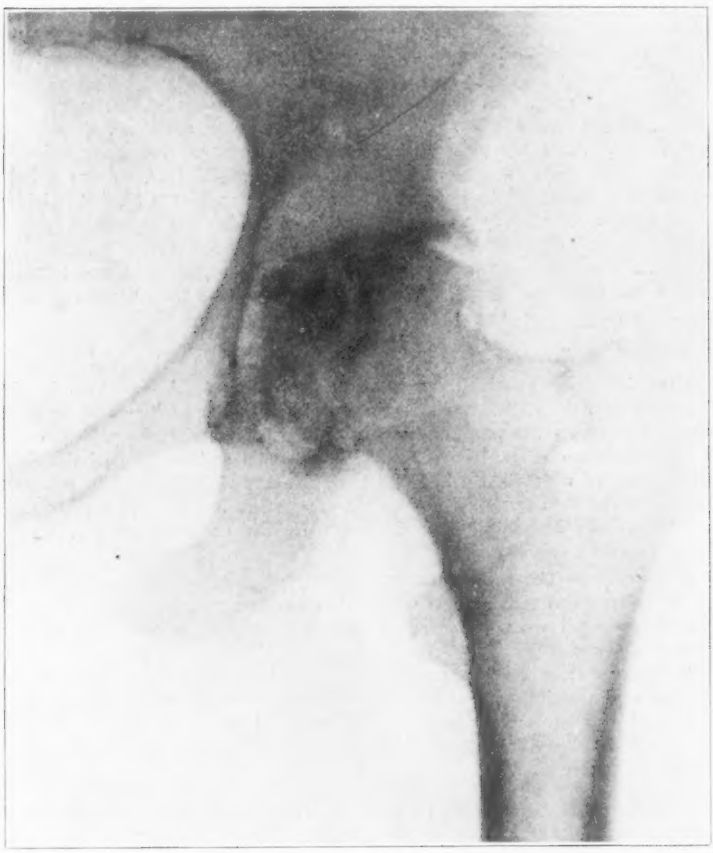

Fig. 3 (case 11).—Hypertrophic arthritis of the right hip. The marked proliferation of the bone about the head of the femur and the acetabulum and the flattening of the head, with areas of absorption, should be noted. The joint space is narrowed.

about the head of the femur and the acetabulum and the flattening of the head, with areas of absorption, should be noted. The joint space was narrowed. An arthrotomy of the right hip was performed on June 13, 1927; as the capsule of the joint was opened, a small amount of turbid, yellow fluid exuded. Culture showed a growth of *Staphylococcus aureus*.

CASE 12.—*History.*—F. N., a man, aged 32, married, was admitted on June 28, 1927, with a complaint of stiffness and pain in the right hip and leg. A diagnosis was made of chronic infectious arthritis of the right hip. For the past sixteen years the patient had recurrent pain and stiffness in the right hip; the pain at times radiated down the leg. About eight months before admission to the hospital, the condition was quite severe, and caused a limping on the right side. Since this time it had gradually subsided.

The patient's health had been excellent. He had colds and sore throat occasionally. Eight years before admission he had a perianal abscess. He denied venereal infection.

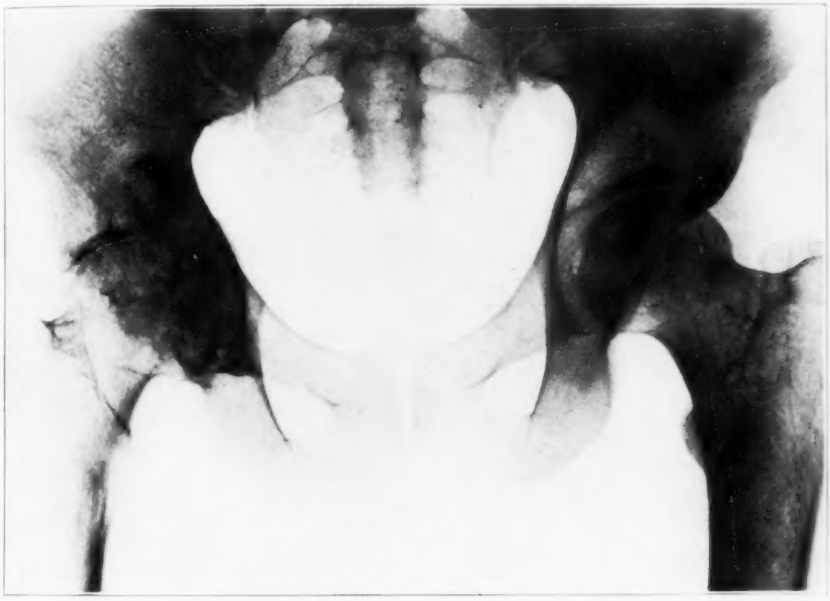

Fig. 4 (case 12).—Marked bony destruction of the right hip. There is a flattening of the epiphysis suggesting a gonorrheal or tuberculous infection, not unlike Perthes' disease. Marked narrowing of the joint space. The marked irregularity about the lower articular portion of the head of the femur, and the areas of absorption through the head and that portion of the ileum immediately above the head, should also be noted.

Examination.—The patient was well developed and well nourished. Enlargement of the lymph nodes was not noted. The tonsils were small, adherent and not inflamed. The sinuses were clear. The teeth were poorly kept. The heart and lungs were normal. The abdomen was normal. The prostate was normal. The right leg was held in slight abduction and external rotation; there was spasm of the adductor muscles, and limitation of flexion and rotation.

Laboratory examination of the blood revealed: white cells, 9,200; hemoglobin content, 85 per cent; lymphocytes, 33 per cent, and monocytes, 1 per cent. The

urine was normal. A Wassermann test was not done. An x-ray picture (fig. 4) of the right hip showed a marked bony destruction with a flattening of the epiphysis, suggesting a gonorrheal or tuberculous infection, not unlike Perthes' disease. There was marked narrowing of the joint space. The marked irregularity about the lower articular portion of the head of the femur, and the areas of absorption through the head and that portion of the ileum immediately above the head should also be noted. Arthrotomy was performed on the right hip on June 30, 1927; as the capsule was opened, a large amount of thin, straw colored fluid exuded. Culture from this fluid showed a moderate growth of *S. viridans.*

Fig. 5 (case 13).—Hypertrophic arthritis of the right knee. The exostoses on the internal condyles of the femur and tibia, with one small loose body opposite, should be noted. Angulation and irregularity are seen about the external condyle of the tibia.

CASE 13.—*History.*—Mrs. L. P., aged 58, colored, was seen in the dispensary on Jan. 5, 1927, with the complaint of pain, tenderness and swelling of the right knee and fourth toe of the left foot. A diagnosis was made of infectious arthritis of the right knee and left foot. The onset had been gradual, over a period of a year, with pain, swelling and stiffness in the right knee and the fourth left toe. These symptoms had become more acute during the last month.

The patient's health had been fair. She was always subject to headaches. A turbinal was removed fifteen years before. Tonsillectomy was performed thirty

years before. She probably had acute rheumatic fever years previously. She had colds frequently. Some indigestion was noted, but bowel movements were regular.

Examination.—The patient was obese and healthy looking, about 30 pounds (13.6 Kg.) overweight. Enlargement of the lymph nodes was not noted. The tonsils had been cleanly removed. The teeth were in fair condition. The heart was slightly enlarged to the left. The lungs were normal. The abdomen was normal. The right knee showed tenderness over the condyles and tuberosities with pain on flexing the joint. Tenderness was felt through the first phalangeal joint of the fourth left toe. The pelvis was normal.

Laboratory examinations revealed the following results: The Wassermann reaction was negative. The urine yielded a slight trace of albumin and sugar. An x-ray picture (fig. 5) of the right knee showed hypertrophic arthritis. The exostoses on the internal condyles of the femur and tibia, with one small loose body opposite, should be noted. Angulation and irregularity were seen about the external condyle of the tibia. Aspiration of the right knee on March 1, 1927, yielded a small amount of normal looking joint fluid. Culture showed a growth of *S. viridans.*

CASE 14.—*History.*—Mrs. M. T., aged 55, was seen in the dispensary on April 20, 1927, with the complaint of pains in the bones and joints of the extremities. A diagnosis was made of chronic infectious arthritis. Twelve years before she had painful, frequent and bloody urine; at that time she first noticed pains in the back and joints. This condition had recurred frequently since the onset, being worse first in one joint and then in the other. At present it was worse in the feet and left arm.

The patient's health had been good. She had typhoid fever thirty years previously. Earache occurred frequently when she was a child. She had sore throat and cold frequently.

Examination.—The patient was large, robust and healthy appearing. Enlargement of the lymph nodes was not noted. The tonsils were small, adherent and not inflamed. The teeth were in good condition. The sinuses were clear. The heart and lungs were normal. The abdomen was normal. No focus of infection was found in the pelvis. The left foot and both knees showed swelling, tenderness and crepitation; there was an increase in fluid in the knees.

Laboratory examinations revealed the following results. An x-ray picture of the right knee showed slight infections arthritis. Aspiration of the left knee on May 5, 1927, yielded 4 cc. of thick, stringy fluid. Culture showed a light growth of *S. viridans.* The cell count was 80. The differential count was: neutrophils, 15.8 per cent; basophils, 2 per cent; monocytes, 56 per cent; macrophages, 4 per cent, and lymphocytes, 22.2 per cent.

CASE 15.—*History.*—Miss C. B., aged 24, was admitted on March 24, 1927, with the complaint of swelling of the joints, especially the right knee. A diagnosis was made of chronic infectious arthritis. The onset occurred in 1918, following an attack of influenza, with pain in the right ankle, right hip and right knee. For the last eight years, she had intermittent swelling of the right knee accompanied by pain through her joints. There was only a slight amount of pain and stiffness in the knee. Four years before admission to the hospital, a synovectomy of the right knee was done; this relieved the condition for about one year, but since that time the swelling had been present.

The patient's health had been excellent. The tonsils and adenoids were removed seven years before. One tooth was extracted eight years previously. She had gingivitis in 1920.

Examination.—The patient was well developed and well nourished. Moderate enlargement of the lymph nodes was noted. The tonsils had been removed. The teeth were in good condition. The heart and lungs were normal. The abdomen was normal. The pelvis was normal. The right knee was swollen, with some limitation of motion and tenderness.

Laboratory examination of the blood revealed: red cells, 4,460,00; hemoglobin content, 82 per cent (Sahli); white cells, 8,400; polymorphonuclears, 74 per cent, and lymphocytes, 26 per cent. The Wassermann reaction was negative. The urine was normal. An x-ray picture of the right knee showed periarticular swelling, with fluid in the joint. The right inguinal gland was excised on March 24, 1927. The culture showed a moderate growth of *S. viridans.* A culture of the right knee joint was obtained at arthrotomy on March 24, 1927. On incision of the capsule, a moderate amount of thick, straw colored fluid was obtained. The culture from this was negative.

The patient was discharged on April 6, 1927.

CASE 16.—*History.*—Mrs. C. B., aged 54, was admitted on March 12, 1927, with the complaint of swollen and painful joints. A diagnosis was made of chronic infectious arthritis. Six years before, the right knee became swollen, contracted and tender. Later, the elbows, wrists and ankles became involved. Two years previously, the process extended to the shoulders and neck. Six months before admission to the hospital, following a series of boils on her right arm, there was some relief from the symptoms in the joints.

The patient's health had been excellent. She had septicemia at the age of 15. Several teeth had been extracted. Iritis, in 1919, cleared up following tonsillectomy performed at that time. Constipation was present. She had cystitis three years before. Hysterectomy was performed sixteen years previously.

Examination.—The patient was well developed and well nourished. Moderate enlargement of the lymph nodes was noted. The tonsils had been cleanly removed. There was an infection of both antrums. Examination of the teeth revealed one slight periapical rarefaction. The heart and lungs were normal. The abdomen was normal. Infection was not found in the pelvis. The right hand, right elbow, right knee and shoulders particularly were involved with swelling, tenderness, limitation of motion and crepitus; the left hand, left elbow, left knee and ankles also were involved.

Laboratory examination of the blood revealed: red cells, 5,200,000; hemoglobin content, 85 per cent (Sahli); white cells, 9,800; polymorphonuclears, 74 per cent, and lymphocytes, 26 per cent. The Wassermann reaction was negative. A trace of albumin was found in the urine. An x-ray picture of the right knee showed marked infectious arthritis. The right inguinal node was excised on March 14, 1927. The culture showed a light growth of *S. viridans.* Aspiration of the right knee on March 14, 1927, yielded about 100 cc. of turbid, straw colored fluid. Culture from this was negative. A culture of the right maxillary sinus was positive for *S. viridans.*

CASE 17.—*History.*—Mrs. L. C., aged 34, was admitted on May 8, 1927, with the complaint of swelling and soreness of all joints. A diagnosis was made of chronic infectious arthritis. The onset had been rather gradual, the condition having started two years before with soreness of the right index finger and the thumb. The hand became sore and ached almost constantly. Six months later, the other

hand was similarly involved. During the past year, there was an extension of the process to the feet, shoulders, back, hips and elbows, with increasing discomfort. She had lost 20 pounds (9 Kg.).

The patient's health had been good. A tonsillectomy was performed several years previously. Many of the teeth were extracted. She had two normal deliveries and no miscarriages. She had leukorrhea.

Examination.—The patient was poorly nourished, and was very much depressed. Moderate enlargement of the lymph nodes was noted. The tonsils had been cleanly removed. The sinuses were clear clinically, but the x-ray pictured showed infection of the antrums. Many teeth were missing; there was one periapical infection. The heart and lungs were normal. The abdomen was normal. Examination of the pelvis revealed a lacerated cervix and chronic cervicitis. The hands and knees were swollen and tender, and had a limitation of motion; the shoulders were tender, with a limitation of motion; the spine was tender, with restricted motion; the hands showed atrophic changes. Laboratory examination of the blood revealed: red cells, 5,450,000; hemoglobin content, 60 per cent (Sahli); white cells, 8,100, and polymorphonuclears, 50 per cent. The Wassermann reaction was negative. An occasional faint trace of albumin was observed in the urine. X-ray pictures of the hands and knees showed infectious arthritis. The right inguinal node was excised on Feb. 11, 1927. The culture showed a moderate growth of nonhemolytic streptococci. Aspiration of the right knee on May 12, 1927, yielded a small amount of slightly turbid fluid. Culture from this did not show any growth. The cell count was 5,720. The differential count was: neutrophils, 57 per cent; monocytes, 24 per cent; lymphocytes, 17.8 per cent, and macrophages, 1.2 per cent.

CASE 18.—*History.*—A. D., a man, aged 53, married, was admitted on March 8, 1927, with the complaint of pain, swelling and deformity of the joints of the hands and knees. A diagnosis was made of chronic infectious arthritis. The onset followed an acute febrile illness in January, 1924, which was called the grip. A few days after this illness pain was felt in the shoulders. A cold taken at this time was followed by pain in the shoulders, neck and right elbow. The hands became weaker. Four months after the onset, the tonsils were removed, resulting in considerable improvement in the arthritis. During the last year, the patient was unable to work because of pain and weakness in the shoulders, elbows and hands.

The patient's health was excellent. He had severe attacks of tonsillitis until the tonsillectomy was performed in 1924. The teeth had given little trouble. He had colds frequently. He had pleurisy twenty years before. He had been troubled a great deal by indigestion. There had been occasional palpitation of the heart. He had not had any venereal disease. Nocturia causing urination from two to three times a night had been present for the last year.

Examination.—The patient was well developed and well nourished. There was moderate enlargement of the lymph nodes, especially in the cervical region. The tonsils had been removed, but the pharynx was injected. The sinuses appeared clear by the x-ray picture. The teeth were in fair condition. The lungs were clear. The heart was slightly enlarged to the left, without murmurs. The abdomen was normal. The prostate was not enlarged. The hands and knees showed considerable tenderness, swelling and limitation of motion. Laboratory examinations of the blood revealed: red cells, 4,100,000; hemoglobin content, 80 per cent (Sahli); white cells, 10,000, and polymorphonuclears, 72 per cent. The Wassermann reaction was negative. The urine was normal. X-ray pictures of

the hands showed infectious arthritis. A cervical node was removed on March 24, 1927. The culture showed a moderate growth of *S. viridans*. Aspiration of the left knee on March 14, 1927, yielded fluid small in amount and of normal appearance. The culture was negative. The cell count was 600. The differential count was: neutrophils, 34 per cent; monocytes, 18 per cent; lymphocytes, 44 per cent; macrophages, 3 per cent, and mast cells, 1 per cent.

The patient was discharged on April 9, 1927.

CASE 10.—*History.*—R. V., a man, aged 62, married, was seen in the dispensary on Oct. 28, 1926, with a complaint of pain and tenderness in the right knee, shoulders, wrists, neck and hands. A diagnosis was made of chronic infectious arthritis. The onset occurred two and one-half years previously, following a trauma of the right knee with the development of pain, swelling, and stiffness. This joint involvement then spread to the shoulders, wrists, neck and hands.

The patient's health was fair. He probably had pulmonary tuberculosis as a child. Twenty-five years before, he had rheumatism in the heels, which spread to the other joints, lasted three weeks and then completely subsided. He had not had sore throat or colds. The teeth were extracted in January, 1925. He had a gonorrheal infection and primary sore twenty-five years previously. He was formerly alcoholic.

Examination.—The patient was poorly nourished. Moderate lymph node enlargement was observed. The tonsils were small and not infected. The sinuses were clear. Examination of the teeth revealed: sepsis with periapical rarefactions, and pyorrhea. The heart and lungs were normal. The abdomen was normal. The prostate was small, and a focus of infection was not observed. The right knee showed swelling, tenderness, limitation of motion and an increase of fluid; the hands and ankles were swollen and somewhat tender. Laboratory examinations disclosed the following results. The Wassermann reaction was negative. An x-ray picture of the right knee showed infectious arthritis. The right inguinal node was excised on Oct. 28, 1926. Culture from this showed *S. viridans*. Aspiration was performed on the left knee on March 7, 1927, and 5 cc. of normal looking fluid was obtained. The culture was negative. The cell count was 500. The differential count was: neutrophils, 82.8 per cent; monocytes, 8.6 per cent, and lymphocytes, 8.6 per cent.

The bacteriologic work reported in this article was done in the laboratory of Dr. Harold L. Amoss; and Dr. J. W. Pierson and Dr. F. O. Coe were consulted in the interpretation of the roentgenograms.

ROENTGEN-RAY THERAPY OF THE HYPOPHYSIS IN A PATIENT WITH ACROMEGALY

ITS EFFECT ON DEXTROSE TOLERANCE *

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The widespread involvement of various organs and tissues of the body in that remarkable disease, acromegaly, has been commented on by many writers. In a monograph detailing the autopsies in four cases, Cushing and Davidoff [1] emphasized the protean manifestations produced by the exaggerated secretion from the anterior portion of the hypophysis. They called attention not only to the extraordinary osseous deformities and "acromegalic myxedema" which hitherto have dominated the clinical picture but also to the pronounced visceromegalies (cardiac, hepatic, renal, splenic, etc.), and to the noteworthy secondary involvement of most of the other ductless glands.

Several publications of late have dealt particularly with the carbohydrate metabolism in acromegaly (for instance, those of Cushing and Davidoff,[2] Colwell,[3] John [4] and Ellis [5]). The incidence of diabetes mellitus in acromegaly has been variously estimated from 9 per cent (Arnold [6]) to as high as 40 per cent (Borchardt [7]). Cushing and Davidoff [2] reported glycosuria one out of four times (25 per cent) in

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* From the Endocrine and Metabolic Clinics of the University of California Medical School.

1. Cushing, Harvey; and Davidoff, L. M.: Studies in Acromegaly: V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph 22, Rockefeller Inst. M. Research, 1927.

2. Cushing, Harvey; and Davidoff, L. M.: Studies in Acromegaly: VI. The Disturbances of Carbohydrate Metabolism, Arch. Int. Med. **39**:751 (June) 1927.

3. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1, 1927.

4. John, H. J.: Spontaneous Disappearance of Diabetes, J.A.M.A. **85**:1629 (Nov. 21) 1925; The Possible Relationship between Acromegaly and Diabetes, Arch.Int.Med. **37**:489 (April) 1926.

5. Ellis, A. W. M.: Hyperglycemia and Glycosuria in Acromegaly with Pathological Report by Prof. H. M. Turnbull, Lancet **1**:1200, 1924.

6. Arnold, J.: Weitere Beiträge zur Akromegaliefrage, Virchows Arch. f. path. Anat. **135**:1, 1894.

7. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66**:332, 1908.

100 personally observed patients. Whatever percentage may be agreed on, it is universally conceded that the association of true diabetes with acromegaly is strikingly frequent and "greater than with any other known disorder."

At this point it may be desirable to contrast the specific and outspoken pathologic condition characteristic of acromegaly, invariably found in the anterior lobe of the hypophysis, namely, a chromophilic adenoma, with the inconstant, meager, and relatively unconvincing changes in the Langerhans tissue of the pancreas, supposedly the seat of diabetes mellitus. From the standpoint of microscopic changes, the origin of acromegaly is constant and settled, whereas the unitary pathogenesis of diabetes mellitus is seriously open to question.[7a]

We may now address ourselves to the hypotheses advanced for the disturbances in carbohydrate metabolism so frequently accompanying acromegaly. They have been conveniently divided under two captions: (*a*) the neurogenic and (*b*) the endocrine.

THE NEUROGENIC HYPOTHESIS

The first explanation was advocated many years ago and still has strong adherents. Thus Colwell,[3] in a recent article, gave as his opinion that the hypophysis is probably without significance in the field of carbohydrate metabolism as a gland of internal secretion. He favored the point of view that important nerve centers or pathways situated near the hypophysis in the hypothalmus are concerned with the control of secretion of insulin. In this connection Cushing and Davidoff [2] pointed out:

> Of the two forms of diabetes, diabetes insipidus, though the rarer, is far more entitled to be considered as a hypophyseal or parahypophyseal symptom than is diabetes mellitus. But when one considers that diabetes insipidus is practically unknown as a complication of pituitary adenomas, whether acromegalic or hypopituitary, no matter how large they grow to be or how much they may chance to deform the infundibulum and third ventricle, we may well pause before ascribing diabetes mellitus to the pressure of a pituitary adenoma against some still more hypothetical nerve center in the neighborhood. And of this we may speak the more emphatically since the far more numerous chromophobe adenomas of comparable size are rarely accompanied by glycosuria.
>
> In short, the size of tumor and the pressure against the brain as a cause of the diabetes can be entirely discounted. The essence of the matter lies in the fact that only one particular variety of adenoma, irrespective of its size, is prone to cause the disturbance of sugar metabolism which may go on to the production of diabetes mellitus. This particular kind of adenoma is that composed of chromophilic cells which accompanies acromegaly.

7a. "The accepted theory of diabetes as a disorder of the islands of Langerhans has found meager substantiation from the anatomic standpoint" (Yater, W. M.: Acromegaly and Diabetes; Report of Six Cases, Arch. Int. Med. **41**:883 [June] 1928).

This brief statement suffices for the purposes of this paper. The reader may pursue this discussion further in the articles already referred to.

THE ENDOCRINE HYPOTHYSIS

It seems unnecessary to implicate the thyroid and the suprarenal medulla in responsibility for acromegalic diabetes mellitus. That both these glands might influence carbohydrate metabolism is recognized, but it appears far fetched and devious to enmesh them in an explanation of hypophyseal diabetes.

The prevalence of hyperglycemia and glycosuria in acromegaly has been referred to, and it is also well known that the reverse states of high sugar tolerance and even hypoglycemia occur commonly in hypopituitarism. The latter phenomena not only have received clinical recognition, but have been confirmed by experimental hypophysectomies.

The endocrine relationship of acromegaly and diabetes mellitus may be considered from three points of view: (1) That acromegaly and diabetes are two separate and distinct clinical conditions; that their occurrence in the same patient is purely coincidental, and that the disturbance in carbohydrate metabolism is primarily and solely due to a lesion or functional impairment of the internally secreting portion of the pancreas; (2) that the hypophysis is primarily and solely responsible for the hyperglycemia, without participation by the pancreas; (3) that the hypophysis plays the leading rôle, but produces alterations in dextrose metabolism by the antagonistic effect of its hormones on secretion of insulin or insulin activity.

The first assumption may be summarily dismissed. It would be a preposterous strain on statistics and the laws of chance to claim an independent and coincident diabetes in from 25 to 40 per cent of acromegalic persons.

The second assumption, which, per contra, would make the hypophysis the sole agent for the hyperglycemia of acromegaly, is an interesting possibility, but remains unproved. No one as yet has succeeded in producing permanent diabetes mellitus by the experimental injections (over long periods) of pituitary extracts.

Potent preparations from the posterior (and intermediate) lobe have been available for many years and have been impressively effective in reducing the thirst and polyuria in diabetes insipidus; in hastening labor by contracting the uterus, and in other clinical states in which a powerful smooth muscle stimulant was indicated. But injections of posterior lobe extract into the experimental animal have failed to produce more than a transient glycosuria and hyperglycemia. Nevertheless, this hormone has its place in the clinical treatment of persons with diabetes because of its antagonistic action to insulin; and this discovery

by Burn [8] has been beneficially utilized in counteracting the hypoglycemic reaction consequent to overdosage with insulin. A hormone which possesses this important characteristic can hardly be considered negligible in the field of carbohydrate metabolism.[8a]

Acromegaly, however, is predominantly and, perhaps, exclusively a disease of the anterior lobe. It arises from a postadolescent hyperactivity of the acidophilic cells. It would seem logical, therefore, to ascribe the accompanying hyperglycemia and glycosuria to this excessive secretion from the anterior lobe. Unfortunately for the purposes of this argument, experimental evidence recording the effects on blood sugar of repeated injections of an active anterior lobe extract has not been published. That a potent extract exists has been demonstrated by Evans [9] in his production of gigantic rats; but whether these animals with hyperpituitarism showed hyperglycemia and glycosuria was not disclosed. Such a report would be trenchantly significant, since gigantism is a preadolescent expression of hyperactivity of the anterior lobe in many respects comparable to the postadolescent manifestations that result in acromegaly.

In this connection, Cushing and Davidoff have pertinently called attention to the not infrequent glycosuria in pregnancy "during which, as first demonstrated by Erdheim and Stumme [10] the hypophysial pars anterior enlarges and takes on additional activity." Another clinical observation of interest is "the recognized peak of diabetes in childhood at about 14 years" which led them to question "whether this is in any way related to a period of unusual activity of the anterior hypophysis."

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8. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and other Substances, J. Physiol. **57**:318, 1923.

8a. Since this paper was written two articles have appeared which deal with this subject: Ulrich, H.: The Antagonism Between Insulin and Pituitary Extract; Its Demonstration in a Patient with Acromegaly, Arch. Int. Med. **41**:875 (June) 1928. Yater, W. M.: Acromegaly and Diabetes; Report of Six Cases, Arch. Int. Med. **41**:883 (June) 1928. Ulrich stated that loss of carbohydrate tolerance in hyperpituitary disease was due to an antagonistic inhibitory action, exercised by excessive pituitary secretion, probably of the posterior lobe, on normal insulin function. He reported a case of hyperpituitary disease with acromegaly and glycosuria in which this antagonistic action was demonstrated, and in which the effectiveness of insulin was much impaired. Ulrich expressed the opinion that this antagonism may vary in different patients and that insulin may therefore show varying degrees of efficiency in the treatment for hyperpituitary loss of carbohydrate tolerance. Yater found that the diabetes in six persons with acromegaly was in all essential respects similar to the ordinary form and responded similarly to diet and insulin therapy.

9. Evans, H. M.: The Function of the Anterior Hypophysis, Harvey Lecture Series, Philadelphia, 1923-1924.

10. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse, Beitr. z. path. Anat. u. z. allg. Pathol. **46**:1, 1909.

Considered singly, these bits of evidence are inconclusive and circumstantial at best, but marshaled together they become intriguing and persuasive. After all, diabetes mellitus is only a clinical syndrome, not a specific disease, and there is justification for the suspicion that a lesion, or even a functional weakness, of the pancreatic islets is not an invariable or indispensable factor.

It must be admitted that, in the present state of knowledge, the third assumption seems the most conservative and the one that best fits the facts. Restated, this hypothesis implies that the hyperglycemia and glycosuria of acromegaly are "primarily hypophyseal, even though the pancreatic islets doubtless play a secondary rôle in their production." [2]

Putting aside the theoretical aspects of this question, which though fascinating are plainly debatable, we may inquire into the effects on carbohydrate metabolism achieved by a direct attack on the acromegalic process itself. Some significant data exist on this point, namely, the effect of hypophyseal operations on sugar tolerance in persons with acromegaly.

In 1924, Ellis [5] recorded the interesting case of a woman, aged 42, who was known to have had acromegaly for ten years. She had shown diabetic symptoms for about eight months with a blood sugar level of 0.43 per cent and with 10 per cent glycosuria, and large quantities of acetone bodies. She became sugar free after three days of fasting, and a limited diet for the following three weeks maintained this condition. The pituitary growth was then partially removed by a transfrontal operation. A trace of glycosuria was found postoperatively, but for the following three years, despite an "increasing laxity of diet," she remained free from sugar in the urine, although a hyperglycemia persisted. How much of this improvement following operation is real and how much is only apparent, but actually due to elevation in renal threshold, cannot be answered. Cushing and Davidoff [2] reported the case of a woman, aged 22, who was first observed in December, 1925, complaining of headaches. She showed osseous evidence of acromegaly, but there was no disturbance of vision and the sella was small. At this time glycosuria was not present, but the blood sugar was 0.13 per cent. When the woman was seen again on Aug. 27, 1926, there was no glycosuria, but on Sept. 2, 1926, she was found to have a glycosuria amounting to 0.7 per cent. The blood sugar on September 10 was 0.14 per cent. Transsphenoidal decompression was performed, September 20, and the tissue removed showed an acidophilic adenoma. She made an excellent recovery with immediate cessation of her headaches and early subsidence of her "pituitary myxedema." Her blood at the termination of the operation on September 20 showed a sugar content of 0.24 per cent; three days later, on September 24, it was 0.12 per cent; on September 28, 0.11 per cent and on October 1, 0.09 per cent. In commenting on these

data, the authors stated that this can hardly be considered a cure of a person with acromegalic diabetes, since the operation may merely have coincided with a wave of melituria, but that the postoperative fall in blood sugar was a significant phenomenon. They further report that in six patients, whose sugar tolerance was studied both before and after hypophysectomy, a definite postoperative lowering in the blood sugar levels was demonstrable. These observations are all the more significant since unusual pains were taken in the determination of the dextrose tolerance, the intravenous method being employed in preference to the ordinary oral procedure, thus insuring greater accuracy. Cushing and Davidoff made the following deductions from these observations:

> (1) That the function of metabolizing carbohydrates is frequently impaired in acromegaly, amounting in many cases to actual clinical diabetes mellitus; and (2) that measures taken to reduce the hyperactivity of the pituitary anterior lobe seemed to have a beneficial effect on the patient's ability to handle sugars. Whether these findings indicate that the hypophysis may directly influence the capacity of the body to utilize carbohydrates, or whether the effect occurs only through some secondary disturbance of the glycolytic function of the pancreatic islets, there is as yet no positive way of determining. We are inclined to favor the latter view, but in either case the hypophysis so far as we can see plays the leading role.

As roentgen rays are known to depress cellular activity, and since this striking effect has been successfully utilized in diminishing the hyperthyroidism of exophthalmic goiter (not only clinically, but also in reducing the basal metabolic rate); since it has come into use as an adjuvant in controlling the size of pituitary tumors (Béclere,[11] Towne[12]), and since in one case at least its use amounted to a cure in a person with diabetes insipidus, it occurred to us that this therapeutic procedure might have some influence in diminishing hyperglycemia in a patient with acromegaly in whom normal vision and normal visual fields precluded the necessity for operative intervention. It is the encouraging outcome of this maneuver that forms the reason for this paper. The case in question is as follows:

REPORT OF CASE

M. M., a Spanish woman, aged 51, married, first came to the outpatient department, Feb. 23, 1926, complaining of headaches, rheumatism, dizzy spells, nocturia, insomnia, dyspnea on exertion and constipation.

She was married at 17 and had three healthy daughters. Her health had been good except for an appendectomy performed when she was 45 years old for an uncomplicated attack of acute appendicitis.

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11. Béclere, A.: Technique, résultats, indications et contre-indications de la roentgenthérapie des tumeurs hypophysaires, Rev. neurol. **38**:808, 1922.

12. Towne, E. B.: Cessation of Diabetes Insipidus on Roentgen-Ray Treatment of Pituitary Gland, J. A. M. A. **83**:2085 (Dec. 27) 1924; Roentgen-Ray Treatment of Pituitary Tumors, Arch. Neurol. & Psychiat. **15**:92 (Jan.) 1926.

Catamenia began when she was 16; the flow was rather profuse, and lasted five or six days. Menopause followed the removal of fibroids, at the age of 45.

The present illness can be divided into two parts. Polydipsia, polyuria and polyphagia had been present for approximately twenty years. These symptoms had gradually increased in severity. Her height was 5 feet (153 cm.); she had gradually become heavier after the age of 20, and her weight had increased from 194 to 204 pounds (88 to 92.5 Kg.) in the past year. For at least twelve years prior to that she had weighed between 190 and 195 pounds (86.2 and 88.5 Kg.).

At about 40 years of age there was a noticeable change in her appearance, and since then there had been a gradually progressive enlargement of the nose, lips, tongue, jaw, malar bones, superciliary ridges, calvarium, hands, feet, ribs and sternum. Accompanying this there had been a gradual loss of strength. Her shoes, gloves and hats now had to be considerably larger than formerly (figs. 1 and 2). About eight years before admission, she began to have headaches which varied in intensity but which were constant in some degree through the day. She was quite nervous in crowds and occasionally somewhat irritable at home. There had been some forgetfulness during the previous year. She had had fre-

Fig. 1.—Appearance of patient at the age of 32 years, before development of acromegaly.

quent drenching sweats above the waist during the past two years and perspired profusely when excited or working. Her hands and feet felt cold, and she had a cold sensation in the back of her neck. For the past ten years she had had pains in her ankles, knees, shoulders, sternoclavicular joints, costocondral region and finger joints. These joints had been swollen and red, and had shown hard, white nodules at times.

The woman was short, dark and obese, with typical acromegalic facies (fig. 2). The skin was thick and rather dry. The hair was coarse and oily, and displayed masculine distribution with a few coarse hairs on the chin and about each nipple, masculine pubic escutcheon, and much hair on the thighs, upper legs and forearms. The head was large, with heavy supra-orbital ridges and zygomatic protuberances. The nose was large and bulbous. The face was broad, with mandibular prognathism. There was spacing of the upper incisors. The tongue was enlarged and thick and showed transverse furrows. The thyroid gland was of normal size, shape and consistency. The chest was barrel-shaped, and the manubrium sternum was prominent. The lungs were normal. The heart was slightly enlarged, and there was a blowing systolic murmur at the apex. Enlargement of the arch was not present. The peripheral vessels were

not palpably thickened. The systolic blood pressure was 125, diastolic, 80. The breasts were large, obese and pendulous. Great folds of skin and fat were present below the costal margin on each side; there was a heavy panniculus adiposus over the abdomen, and the hips and thighs were huge. The legs were less obese (fig. 2). The feet and hands were broad, thick and spadelike (fig. 3).

The Wassermann test of the blood was negative. The specimen of urine was clear, with a specific gravity of 1.009, and did not reveal any abnormalities in routine examination. The average daily fluid intake and output for three days on an unrestricted diet was 2,750 cc. The phthalein output was 50 per cent for

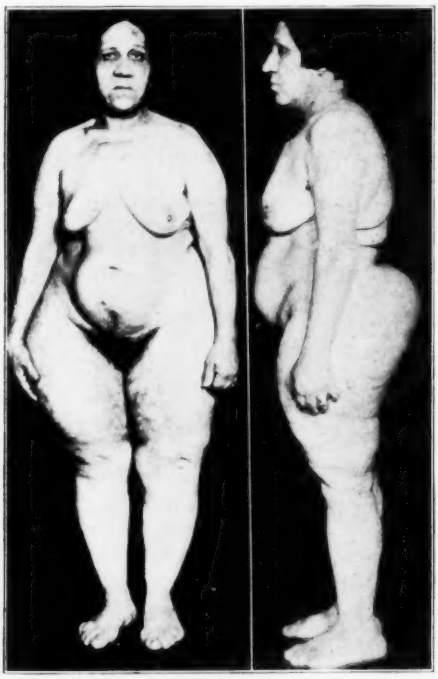

Fig. 2.—Front view and profile of acromegalic patient, aged 51 years, prior to dietetic therapy. The enlargement of the end of the nose, deep nasolabial folds, massive jaw, sternal protuberances, mild cervicodorsal kyphosis, broad feet, enormous girdle obesity and heterosexual pubic escutcheon should be noted.

two hours. The blood count and routine examination of the stools gave negative results. The basal metabolic rate was 12.7 per cent plus.

Roentgenograms of the skull showed the sella turcica to be oval and well roofed over by the anterior and posterior clinoid processes which closely approximated each other. The skull showed thickening of the calvarium, proliferation of the cranial air sinuses, and prognathism, characteristic of acromegaly.

Tests of the vestibular apparatus did not reveal any abnormalities.

Repeated examinations of the eyes on March 8, 1926, March 17, 1927, and July 14, 1927, did not show constriction of the visual fields and signs of increased intracranial pressure. The fundi showed the typical yellow disks of acromegaly, and the nasal half of each disk was somewhat hyperemic.

On May 25, 1926, the dextrose tolerance test (oral method, 100 Gm. of dextrose being used) showed a fasting level of 0.119 per cent; a half hour after the administration of dextrose, 0.214 per cent; one hour after the administration of dextrose, 0.300 per cent, and two hours after the administration of dextrose, 0.234 per cent. Sugar did not appear in the urine at any time during the two hour test, indicating a high kidney threshold. It was determined at first to treat the patient as if she had an ordinary case of diabetes mellitus.

Under a quantitative dietary regimen, which kept the blood sugar within the normal zone and which reduced her weight from 93 Kg. (204.6 pounds) to 65.5

Fig. 3.—Appearance of patient's acromegalic spade hand as compared with the hand of a normal control.

Kg. (144.1 pound) in nine months, there was general physical improvement (fig. 4). Polydipsia, polyuria and polyphagia disappeared within three days after treatment was started. Headaches became mild and infrequent. She became happier and more active and energetic. A second dextrose tolerance test done at the end of this period (Feb. 9, 1927) did not show definite improvement in the glycemia curve (fasting — 0.120 per cent, half hour after dextrose, 0.285 per cent; one hour after dextrose, 0.275 per cent and two hours after dextrose 0.227 per cent) but demonstrated definite improvement in the renal threshold, qualitative tests on the one hour and two hour specimens of urine showing traces of dextrose.

This lowering of renal threshold to a point near the normal level is frequently seen in the treatment of patients with ordinary forms of diabetes mellitus. The occurrence of such a reduction in this case would indicate that the pituitary gland does not have any influence on renal threshold, and therefore these patients

will show glycosuria when their blood sugar goes above their renal threshold, provided the urine is not too dilute to give a positive test with the ordinary reagents.

In view of the lack of improvement in dextrose tolerance, despite adequate dietary control of the diabetes, further treatment was directed toward the acromegalic condition per se, by instituting two courses of roentgen-ray treatments to the hypophysis.

One month after the first course of roentgen-ray therapy, another dextrose tolerance test was made and some improvement could be seen. This third test showed: fasting — 0.118 per cent; a half hour after dextrose, 0.194 per cent; one hour after dextrose, 0.258 per cent; two hours after dextrose, 0.215 per cent. The maximum height of glycemia was 0.258 per cent as compared with 0.285 per cent, which was the lowest maximum of the two previous tests; and the two hour level was down to 0.215 per cent as compared with 0.227 per cent and 0.234 per cent in the tests prior to roentgen-ray treatment. The renal threshold showed further reduction, in that dextrose was present as a moderate trace in the half hour specimen, and in heavy traces in the one hour and two hour specimens.

The fourth dextrose tolerance test made on Sept. 15, 1927, four months after the first course of roentgen-ray therapy, showed a height of only 0.236 per cent,

Dosage and Technic

Date		Skin Target Distance	Filter	Spark Gap	Milliampere Minutes
4/12/27	Left side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	150
4/15/27	Right side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	150
5/16/27	Right side	12 inches	¼ mm. copper 1 mm. oluminum	9 inches	75
5/24/27	Left side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	75
9/28/27	Right side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	120
10/ 3/27	Left side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	120
10/14/27	Right side	12 inches	¼ mm. cooper 1 mm. aluminum	9 inches	120
10/21/27	Left side	12 inches	¼ mm. copper 1 mm. aluminum	9 inches	120

and the two hour level was within the normal zone, being 0.105 per cent (fasting, 0.124 per cent; a half hour after dextrose, 0.206 per cent; one hour after dextrose, 0.236 per cent, and two hours after dextrose, 0.105 per cent). There was no gross evidence of further improvement in renal threshold.

During the entire period of roentgen-ray therapy and in the four month's interval between the two courses of treatment, the diet remained the same as in the previous nine months of dietary treatment alone (protein, 70; fat, 120; carbohydrate, 60; calories, 1,600). The weight fluctuated between 144 and 149 pounds (65.3 and 67.6 Kg.).

A second course of four roentgen-ray treatments to the hypophysis was then instituted, and the fifth dextrose tolerance test, one month later, Nov. 29, 1927, gave the following values: Fasting — 0.126 per cent; half hour, — 0.216 per cent, one hour, 0.183 per cent and two hours, 0.147 per cent. A comparison of these five curves has been charted in figure 5, and presents evidence of progressive improvement since roentgen-ray therapy was instituted.

In September, 1927, the patient was photographed again, and figure 4 shows the same osseous acromegalic characteristics, as was to be expected, but reveals the great loss of weight achieved by the dietary treatment.

In October, 1927, following the second course of roentgen-ray therapy, the patient volunteered the information that her headaches were still further reduced in frequency and severity. A roentgenogram (fig. 6) of the skull taken at this

time showed some enlargement of the sella with thin floor, large sinuses and marked thickening in the frontal region. A roentgenogram of the hands (fig. 7) showed short, heavy metacarpals, except the second, which was about normal. The phalanges were short and the terminal segments were characteristically tufted.

The eye fields were still normal as late as Nov. 22, 1927. It might be stated that the perimetric studies were performed carefully by Dr. Crawford, various sized test objects, and both artificial illumination and sunlight being used.

Apparently the roentgen-ray therapy did not have any effect in reducing the basal metabolic rate, which was 13.2 per cent plus on Nov. 8, 1927.[12a]

Fig. 4.—Front and profile views of patient following nine months of diabetic dietary regimen, resulting in a loss of 60 pounds (27.2 Kg.). Compare with figure 2.

12a. A third basal metabolic rate was taken in June, 1928. It proved to be 3.5 per cent plus. A third course of roentgen-ray treatments to the hypophysis had been given in April, 1928. A sixth dextrose tolerance test was made June 19, 1928: fasting, 0.110 per cent; a half hour after dextose, 0.205 per cent; one hour after dextrose, 0.222 per cent and two hours after dextrose, 0.155 per cent. The third course of inhibitory roentgen-ray therapy seemingly reduced the basal metabolic rate, but failed to effect any further increase in dextrose tolerance.

COMMENTS AND CONCLUSIONS

The experience detailed seems to warrant the following deductions: 1. As noted by others, hyperglycemia without glycosuria may occur in acromegaly, as in ordinary diabetes mellitus. 2. The sugar tolerance in acromegaly may be unaffected by adequate dietary management. 3. Roentgen-ray therapy to the hypophysis in acromegaly may favorably influence dextrose tolerance.

We anticipate the following criticisms:

1. The diabetes of acromegaly differs from ordinary diabetes mellitus by reason of its "fluctuating character"; and whereas a complete cure of persons with true diabetes has never been accomplished (stoppage of

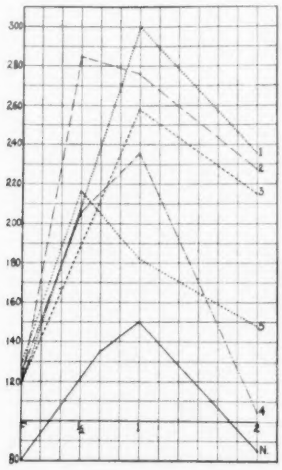

Fig. 5.—Composite chart depicting the five dextrose tolerance curves of the acromegalic patient, together with a normal curve for comparison. (The latter is marked *N.*) The sequence of the curves is indicated by the numerals on the right side. The initial point of each curve represents the fasting level; the second point is the level one-half hour, the third point one hour, and the end point two hours, respectively, after dextrose was given. For further details see test in text. The striking feature of this chart is the progressive lowering of the blood sugar levels consequent to roentgen-ray radiation of the hypophysis.

insulin and unrestricted diet without hyperglycemia), spontaneous cure of acromegalic diabetes has occasionally been observed.[12b] The beneficial effect of the roentgen-ray therapy in our patient may be contested for

12b. Yater (cited before) concluded that "the only difference between diabetes alone and diabetes associated with acromegaly is its occasional spontaneous temporary or permanent disappearance, a point which has been demonstrated in relatively few cases."

this reason, and it may be argued that the lowering of the blood sugar curve merely coincided with a spontaneous remission of her acromegaly. In this connection, we desire to call attention to the following points: (*a*) During nine months of dietary therapy, the blood sugar remained constantly between 0.10 and 0.12 per cent, but dextrose tolerance was uninfluenced until roentgen-ray therapy was instituted; (*b*) during the subsequent nine months' period of unchanged diet plus roentgen-ray therapy, a progressive improvement of dextrose tolerance was noted,

Fig. 6.—Lateral roentgenogram of the skull of patient shown in figures 2 and 4. The enlargement of the sella with thin floor, large sinuses, thickening of the calvarium, especially in the frontal region, and prognathism should be noted.

as is depicted in figure 5, and (*c*) there was no other clinical evidence of diminished activity of the anterior lobe, and the basal metabolic rate was still slightly above normal. This mild elevation of the basal metabolism in acromegalic patients has been recently emphasized by Cushing and Davidoff,[13] as has also the reverse state of an abnormally low

13. Cusing, H., and Davidoff, L. M.: Studies in Acromegaly. IV. The Basal Metabolism, Arch. Int. Med. **39**:673 (May) 1927.

basal metabolic rate in verified cases of hypopituitarism. If a lowering of the basal rate by either hypophysectomy or inhibitory roentgen-ray therapy is a gage of activity of the anterior lobe in acromegaly, then our case would seem to have been uninfluenced; but at least this would seem to answer the objection that the sugar tolerance was raised by a spontaneous reduction of the acromegalism.

Fig. 7.—Roentgenographic appearance of the patient's hand. The short, heavy metacarpals, short phalanges and characteristic terminal tufting should be noted.

2. The second criticism might be that it is false reasoning to ascribe the improvement in dextrose tolerance to the irradiation of the hypophysis, since such improvement may gradually occur during a long dietary regimen, and that our patient was continually on a restricted diet. To this we would rejoin that this improvement did not appear during nine months of dietary management, which is unusual in ordinary diabetes mellitus; and that this improvement promptly followed the roentgenization of the hypophysis.

3. The third objection that might be raised concerns the use of the alimentary method for the determination of dextrose tolerance, as a criterion of improvement. Although we admit that the intravenous administration of dextrose is a more accurate procedure for research purposes, we are inclined to believe that the variability in the degree of absorption of sugars given by the oral method is of minor character, and would not account for the progressive decline in blood sugar levels noted in the case reported. Furthermore, it must be conceded that the oral method is the customary one employed by most authorities on diabetes.

This has been our first experience and, so far as we are aware, the first to be published, of the effect of roentgen-ray therapy of the hypophysis on dextrose tolerance. The results have been sufficiently encouraging to warrant its further use in this patient, in the hope of finally attaining a normal or subnormal blood sugar curve. When this has been accomplished, it will be interesting to watch developments when the patient is released from a low dextrose intake. If the curve remains normal under such conditions, we may feel justified in assuming that the patient's abnormal response to dextrose was directly, or at least primarily, due to the exaggerated secretion from the pituitary pars anterior.

SYPHILIS OF THE STOMACH

WITH SPECIAL REFERENCE TO CERTAIN DIAGNOSTIC CRITERIA*

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Some time ago (1925), one of us (F. D.) resected the distal one third of a stomach which was thought to be the seat of a carcinoma. From the gross and microscopic appearances of the specimen, together with the clinical history, we considered the changes to be syphilitic. In the sections examined, we failed, however, to demonstrate the presence of either *Spirochaeta pallida* or the classic gumma (the term "classic gumma" will be defined later). Two experienced pathologists who were consulted at the time did not consider sufficient evidence of syphilis to be present to justify an anatomic diagnosis of syphilitic gastritis. We entertained no doubt as to the correctness of their opinion and discarded our original conclusions without hesitation.

More recently one of us (H. A. S.) has had the opportunity of studying three similar specimens. Two were resected by Dr. K. A. Meyer at the Cook County Hospital and the third by Dr. C. A. Hedblom at the Research and Educational Hospitals of the University of Illinois. In all three cases, the clinical and laboratory data and the associated lesions (hepatic gummas), found at postmortem observation of one, pointed to syphilis as the etiologic factor of the gastric lesions. Attempts to discover *Spirochacta pallida* or classic lesions in the tissues sectioned were uniformly unsuccessful. The same pathologists were again consulted, with the same outcome, namely, that in their opinion there was insufficient evidence on which to base the diagnosis of syphilis of the stomach.

We desired to know how many of the cases reported and generally accepted as syphilitic gastritis were actually proved according to the criteria prescribed by the two pathologists mentioned. In order to gratify this desire, it became necessary for us to undertake an independent inquiry, the results of which are recorded. We considered as proof of the existence of syphilis of the stomach the demonstration of either the spirochete of syphilis or the classic gumma.

The entire literature on acquired syphilis of the stomach contains only one case in which the bacteriologic observations in the tissues led to

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its acceptance as a proved instance of syphilitic gastritis. In 1922, McNee [1] reported the presence of unusual lesions which he regarded as syphilitic, in a stomach removed at postmortem. From the involved area, eight blocks of tissue were excised and stained according to the Levaditi method. McNee's description reads:

> In sections from one block only, spirochaetes were discovered in great numbers penetrating deeply in the actively growing granulomatous tissue. Near the free surface the spirochaetes in the necrotic layer were mixed with other organisms, but in the deeper granulation tissue close to the muscular coat they were unaccompanied by any other demonstrable organism. They had the typical appearances of *Treponema pallidum*, having from eight to fourteen small and regular curves.

McNee's case is generally quoted as the only one of acquired syphilis of the stomach in which *Spirochaeta pallida* has been demonstrated. So far as we have been able to ascertain, no one has challenged McNee's opinion as to the type species of *Spirillum* in his sections. It seemed rather odd to us that of all the attempts to demonstrate *Spirochaeta pallida* in cases of acquired syphilitic gastritis, McNee's alone should be crowned with success. This circumstance in itself, however, did not raise any question in our minds as to the correctness of his observation. What led us to doubt the diagnosis as to the type of *Spirillum* present was the fact that the organisms were so plentiful. Any worker who has at one time or another engaged in the search for spirochetes in acquired tertiary lesions of syphilis is well aware of the paucity of organisms and the patient search which is required to find even two or three. In one microscopic field of McNee's Levaditi preparation, at least eighteen distinct spirochetes are represented. Such pictures are not infrequently encountered in congenital syphilis, but rarely if ever in acquired tertiary lesions.

In order to differentiate between certain types of spirochetes, the use of the dark field is practically essential. When the examination is limited to the appearance of the organisms in tissues, little weight can be placed on the distinguishing features. The pictures of the spirochetes by McNee are similar, if not identical, with those of Vincent as found for instance in tissue which is the seat of a saprophytic infection. The resemblance is readily recognized when comparison is made between the organisms in McNee's illustration and those demonstrated by Pilot and Davis [2] in sections of tissue of the lungs taken from

1. McNee, J. W.: Syphilis of the Stomach, Quart. J. Med. **15**:215, 1921-1922.

2. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochetes, Arch. Int. Med. **34**:313 (Sept.) 1924. (Especially figures 4 and 11.) Pilot, I.; Davis, D. J., and Shapiro, I. J.: Studies on Fusiform Bacilli and Spirochetes, Am. Rev. Tuberc. **8**:249 (Nov.) 1923 (fig. 4).

patients with pulmonary abscess and gangrene. In their work on pulmonary fusospirochetosis, Pilot and Davis confirmed the observation of others that there occurs beyond the area where fusiform bacilli are found in association with spirochetes an advance zone in which spirochetes alone are present. These observations appear to be identical with those described by McNee, for, according to his report, "the spirochetes in the necrotic surface layer were mixed with other organisms."

The frequency of spirochetes in ulcerating lesions of the stomach is too well known to require emphasis here. Based on his study of the presence of spirochetes in carcinoma, Simmonds [3] concluded that these organisms demanded attention because of the possibility of confounding them with *Spirochaeta pallida*. Fraenkel,[4] in discussing Simmonds' paper, pointed out that from the photomicrographs which portrayed the spirochetes alone, a differentiation could not be made between the spirochetes found in carcinoma and the causative organisms of syphilis. This view is substantiated by the careful bacteriologic studies of Arnheim.[5]

In the case report to follow, a number of spirochetes were found in Levaditi preparations made from the ulcerated areas. These organisms were present on the whole in association with fusiform bacilli and other bacteria. Occasionally, however, spirochetes were found beyond the zone of bacterial invasion. We classified these spirillums as *Spirochaete vincenti* and are inclined to place the organisms found by McNee in the same category. We accept McNee's case as one of gastric syphilis, not on the basis of the bacteriologic observations, but because we consider the anatomic changes sufficiently characteristic to warrant this diagnosis. As a result of the investigation carried out in connection with our cases and those published in the literature, we were led to conclude that the causative organism of syphilis has not been demonstrated in any instance of gastric syphilis reported.

Before entering on a discussion of syphilitic lesions in the stomach, we desire to direct attention to current conceptions of the pathologic anatomy of syphilis in general. An authoritative and clear exposition of the subject is furnished by MacCallum,[6] who, in discussing the pathologic condition of the tertiary stage, stated:

> The most characteristic, though not the most common manifestation of the affects of the spirochaetae in this stage of the disease is the gumma, which receives its name from its elastic, rubber-like consistency (Gummigeschwulst).

3. Simmonds: Ueber Spirochätenbefunde in Karzinomen, München. med. Wchnschr. **55**:1103, 1908.

4. Fraenkel, E.: Discussion on Simmonds (footnote 3).

5. Arnheim, G.: Die Spirochäten bei Lungengrän und ulzerierendem Carcinom (Kulturversuche), Centralbl. f. Bakteriol. **59**:20, 1911.

6. MacCallum, W. G.: A Text Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 708.

Most commonly such nodules are found embedded in the tissue and surrounded on all sides by radiating fibrous tissue which in itself is not especially peculiar. But the central portion is firm, elastic, opaque and yellowish-white like hard cheese. This is the necrotic caseous part, analogous to that found in tubercles but different in its elastic, firm consistency and in the slighter tendency to liquefy. In it one may sometimes discern faint outlines of pre-existent tissue now necrotic. . . . Such nodules may be of almost any size from middle points to large masses. In the miliary gummata there may be no caseation or coagulative necrosis and the nodule is seen as a more or less concentrically arranged group of epithelioid cells richly mingled with mononuclear wandering cells and occasionally with giant cells. The arrangement is usually indefinite and irregular, lacking the sharpness and precision of the architecture of the miliary tubercle.

The impression is gained from the foregoing quotation and from other textbook descriptions that the term gumma may be correctly applied to practically any circumscribed chronic granulomatous lesion occurring in syphilis irrespective of size or the presence or absence of caseation. However, there is a definite tendency on the part of pathologists to choose as the most distinctive lesion of syphilis that type of gumma pictured by MacCallum in a testis (p. 706) and referred to by Kaufmann [7] as fully developed. In this mature lesion, both the gross and microscopic features are unique. In histologic sections as stated by Kaufmann, one can distinguish three zones, namely: (1) a caseous center the result of coagulative necrosis, (2) a middle zone of fibrous tissue with a limited number of recently proliferated and infiltrated cells and (3) an outer layer of younger granulation tissue rich in inflammatory elements. Macroscopically, when of sufficient size, the fully developed gumma yields a rubber-like consistency, and therefore represents a true "gummigeschwulst" seen especially in the liver, brain and testis. It is this particular type of gumma which, when present, is of the greatest value in identifying the infection as syphilitic and in separating the syphilitic from other types of granuloma. As the lesion described may be considered the most characteristic of tertiary syphilis, it is referred to as the "classic gumma."

A painstaking search through the literature on gastric syphilis failed to disclose within the stomach a single instance of a gumma answering to the gross and microscopic description of the fully developed one. Even the certain or almost certain cases of gastric syphilis gathered by Konjetzny [8] in his comprehensive treatise on the subject lack cases showing classic gummas. Analysis of the original reports referred to by

7. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7 and 8, Berlin, 1922, vol. 8, p. 1586.

8. Konjetzny, G. E.; Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, 1928, vol. 4, pt. 2, p. 1026.

Konjetzny (Klebs,[9] Cornil and Ranvier,[10] Birch-Hirschfeld,[11] Fraenkel,[12] Buday,[13] Stolper,[14] Brams,[15] McNee [1]) indicates that the gummas mentioned by those authors were almost invariably found to be circumscribed foci of granulation tissue densely infiltrated by inflammatory cells, but devoid of central necrosis en masse (in Brams' article the microscopic changes of his case are splendidly described and profusely illustrated).

Although classic gummas were absent in the stomachs, they were encountered in other organs, such as the liver, in more than a majority of the cases mentioned. If the gastric lesions recorded were actually syphilitic in origin, then the lack of classic gummas in those stomachs is to be explained on the basis of differences in the local response to the spirochetal invasion of this organ as compared with other organs.

A number of authors believe that the diagnosis of syphilis cannot be positively made on the basis of a single lesion, since, in their opinion, identical morphologic changes may result from another type of infection, for instance, tuberculosis. Pathologists in general choose to speak of the gumma as the characteristic rather than the specific lesion of syphilis, inferring thereby that this particular type of granulomatous tumor occurs most frequently but not invariably in syphilitic lesions. If, however, any single lesion is to be considered specific of the tertiary stage of syphilis, the classic gumma is entitled to first claim. In the following paragraphs, the term specific lesion of syphilis refers to the classic gumma with the tacit understanding that specificity is assumed rather than proved.

As *Spirochaeta pallida* and the classic gumma, which represent respectively the specific organism and the lesion, constitute the only proofs of syphilis, we are forced to conclude that as far as we were able to ascertain, the medical literature does not contain a report of a true case of syphilis of the stomach. This conclusion, however, should not be

9. Klebs, E.: Handbuch der pathologischen Anatomie, Berlin, 1869, vol. 1, pt. 1, p. 260.

10. Cornil, V., and Ranvier, L.: Manuel d'histologie pathologique, ed. 3, Paris, 1912, vol. 4, p. 482.

11. Birch-Hirschfeld, F. V.: Lehrbuch der pathologischen Anatomie, ed. 4, Leipzig, 1895, vol. 4, p. 642.

12. Fraenkel, E.: Zur Lehre von der acquirirten Magen-Darm-Syphilis, Virchows Arch. f. path. Anat. **155**:507, 1899.

13. Buday, K.: Ueber einen ungewöhnlichen Fall von Syphilis, Virchows Arch. f. path. Anat. **141**:514, 1895.

14. Stolper, P.: Beitrage zur Syphilis visceralis (Magen-Lungen-Herzsyphilis), Bibliotheca medica, Cassel, 1896, no. 6, pt. C.

15. Brams, W. A.: Ueber das Ulcus syphiliticum multiforme ventriculi, Arch. f. Verdauungskr. **27**:375, 1921.

construed to mean that the diagnosis of syphilis of the stomach in all cases reported as such is erroneous. As a matter of fact, evidence of gastric syphilis is so convincing in many of the reported cases that for clinical purposes they may be readily accepted as such even in the absence of actual proof.

We do not see any valid reason why the demonstration of the specific organisms in suspected cases of gastric syphilis should be demanded when it is generally conceded that *Spirochaeta pallida* is found in the lesions of acquired tertiary syphilis only exceptionally (Aschoff [16]). Nor do we see the logic of refusing to recognize as syphilis of the stomach a case in which classic gummas are lacking, since it is well known that the gummy tumor with central necrosis en masse is far less common than the less typical lesions of syphilis, and that, furthermore, in not a few locations the classic gumma is rarely seen (aorta, periosteum).

Throughout the body, granulomatous lesions are diagnosed as syphilitic on the basis of collective evidence even in the absence of specific indications. As experienced a pathologist as Fraenkel [17] recommended in cases of questionable syphilitic aortitis the performance of the Wassermann test postmortem, as an aid in final diagnosis. MacCallum [6] writes:

> The history of the case, the Wassermann reaction, the bacterial findings, the distribution of the lesions and their relationship to lesions elsewhere, their size, consistency, and gross appearance, their tendency to heal or to break down, and least of all their histological structure—these are the things upon which the diagnosis of syphilis in the tertiary stage may be based.

We are of the opinion that the standards which are customarily used in the diagnosis of syphilis elsewhere should be applied also to syphilis of the stomach, and that the critical pathologist should require simply a preponderance of evidence and not actual proof before accepting the case as one of gastric syphilis.

After reaching the foregoing conclusions regarding criteria for the diagnosis of syphilis of the stomach, we reviewed the facts in connection with our case of 1925. As a result of this later study, we felt that, in the light of our recently acquired knowledge and opinion, there was sufficient evidence to justify the diagnosis of syphilis of the stomach. We are presenting the case in some detail in order to give the reader an opportunity to judge for himself as to whether or not there are sufficient clinical, laboratory and pathologic data on which to base the diagnosis of syphilitic gastrititis.

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16. Aschoff, L.: Pathologische Anatomie, ed. 6, Jena, 1923, vol. 1, p. 571.

17. Fraenkel, E., and Much, H.: Das Wassermansche Reaktion and der Leiche, München. med. Wchnschr. **55**:2479, 1908.

REPORT OF CASE

Clinical History.—C. D., a colored man, aged 38, was admitted to the medical service of the Cook County Hospital on Aug. 21, 1924, with an examining room diagnosis of gastric syphilis. His presenting complaint was epigastric distress, which had begun eleven months prior to entrance. During the first nine months of the patient's illness, the distress although persistent had been relatively mild. At the beginning of the tenth month, the discomfort had been felt as an actual pain which had caused the patient to stay in bed, where he had remained for approximately four weeks. After his confinement, he had attempted to return to work, but had been compelled to remain home on acount of the pain he experienced.

He had a burning pain accompanied at times by severe cramps. It was located in the epigastrium to the left of the mid-line and was circumscribed. The pain was felt on arising and was relieved for half an hour or so by breakfast. The same pain-food-ease sequence occurred in connection with the other meals. The relief from taking of food, however, was not constant. Pain at night had not been felt prior to entrance. The intake of soda was not followed by definite relief, but by vomiting which occurred usually after the noon meal had been eaten. Pressure applied to the epigastrium allayed the severity of the pain. Relationship was not noted between the pain and the quantity or quality of the food eaten.

The patient had lost 20 pounds (9 Kg.) during that part of his illness previous to six weeks before hospitalization. During these six weeks, he had regained 10 pounds (4.5 Kg.). Constipation had been marked throughout the eleven months, and the patient had required a cathartic in order to obtain a bowel movement. Other noteworthy complaints were not elicited in the routine inventory of symptoms by systems. He had contracted gonorrhea six times. In May, 1923 he had had multiple penile sores followed by bilateral bubo. He believed that the Wassermann reaction had been negative at that time. His occupation necessitated the handling of paint.

Examination.—Physically he was well developed but somewhat undernourished. Abnormalities were not present, except for a slight generalized lymphadenopathy and multiple scars on the glans penis. The chemical analysis of the blood disclosed a moderate degree of secondary anemia. The diagnosis of chronic plumbism was regarded as the most likely, and the patient was placed on a treatment with phosphoric acid and potassium iodide, pending the results of further tests. The Wassermann reaction was reported *2* plus; on the basis of this report, mercury rubs and potassium iodide were prescribed. Sixty cubic centimeters of material with a free acidity of 12 and a total acidity of 35 degrees was aspirated one hour after the administration of an Ewald test meal. Occult blood was not detected in the gastric contents. Tests of two stools, one liquid and the other formed, were negative for chemical blood.

X-ray examination revealed: The stomach proper appeared normal during the screen study, but on the plate series lacked the perfect rounding of the pyloric end. A satisfactory duodenal bulb was not seen at any time. During the early part of the screen examination, a persistent pocket-like shadow was obtained at the right extremity of the base of the cap. There was a marked imperfection of the bulb which was fairly constant in the plate series. The diagnosis was duodenal deformity of sufficient degree to support a clinical determination of ulcer.

Course of Illness.—The case was managed like cases of ulcer, and although the acidity was readily controlled, the pain persisted and was particularly noticeable during the night. After twenty-six days of trial, the Sippy ulcer regimen was discontinued, and nonspecific protein therapy was instituted. This afforded only temporary relief. The patient left the hospital on Oct. 3, 1924, slightly improved.

Approximately three months later, he returned to the hospital, saying that the epigastric pain had increased progressively in severity. On physical examination, tenderness was elicited in the left epigastric region, where resistance was felt. An Ewald test meal yielded 240 cc. of gastric contents, which showed 12 free and 23 combined degrees of acidity. Chemical blood was not found. The motor meal indicated retention after six hours, and the test for occult blood at this time was positive. Of six stools examined for blood, three showed a trace with the benzidine test, the others proved negative. A smear of the bacteria in the stool showed a preponderance of the gram-negative flora. A second x-ray examination on Jan. 12, 1925, disclosed a 4 ounce residue at the end of six hours and a pyloric defect which was interpreted as carcinomatous. The patient was transferred to the surgical service, with the diagnosis of carcinoma of the stomach. On January 19, exploration was undertaken by one of us (F. D.), and an indurated mass of unusual character occupying the pyloric area was palpated. Resection of the distal one third of the stomach was decided on and was carried out according to the Polya method. At the conclusion of the operation, as the patient was being moved from the table, he died suddenly. The mode of death resembled that which occurs in persons with latent syphilis of the brain who are subjected to general anesthesia (LeCount and Singer[18]). The coroner's physician, without making a postmortem examination of the body, attributed death to ether anesthetic.

Pathologic Report.—The gross description read as follows: This specimen consisted of the resected pyloric portion of the stomach to which was attached the beginning duodenum. The specimen, which had the form of a thick, narrow tube, measured 11 and 6.5 cm. along the greater and lesser curvatures, respectively. There was only a small amount of fat in the gastrocolic and gastrohepatic omentums. The lymph glands along the greater curvature were enlarged to the size of a bean, were firm in consistency and on section were a pale pink. The serosa covering the distal half of the specimen was white in places because of fibrous thickening. When opened along the greater curvature and viewed from the mucosal side, three irregular defects in the gastric lining were observed. The largest, which was located on the lesser curvature, extended to involve both anterior and posterior walls, and assumed a form somewhat suggestive of a cloverleaf. It measured 3.5 cm. in its larger and 2.8 cm. in its smaller diameter. The other ulcers located distally were approximately of equal size, and measured 2.4 and 2.2 cm. in diameter, respectively. The largest of the three ulcers was serpiginous in outline, and, as compared with its extent, was quite shallow and superficial. The edges were not thickened or undermined, but were clearly demarcated from the surrounding mucosa and were adherent to the well outlined margins of the ulceration. The floor was smooth and covered with a grayish red membranous deposit which was easily removed. The two smaller ulcers were similar in all essentials.

18. LeCount, E. R., and Singer, H. A.: The Hazard of Surgical Anesthesia with Syphilis of the Brain, J. A. M. A. **84**:358 (Jan. 31) 1925.

The mucous membrane between the ulcerations was for the most part unattached to the underlying submucosa, and was mammilated and devoid of rugous folds. The gastric wall was greatly thickened, beginning at a point 1.6 cm. distal to the proximal edge of the resected specimen and extending to the pyloric ring. The ulcers were located in the thickest portion of the specimen. On section, the thickening was seen to be due mainly to an increase of the submucosa which appeared white and succulent with whitish-yellow miliary and submiliary foci here and there. A number of sectioned blood vessels stood out prominently. The point of maximum thickness measured 1.8 cm., of which the submucosa comprised one half. The thickening gradually decreased in passing centrifically from the zone of ulceration. The muscular layer was only slightly thickened, but was rendered somewhat prominent by contrast with the white submucosa. Distinct connective tissue septums were not seen to pass downward from the submucous to the subserous layer.

Microscopic Description.—Blocks were removed from many regions, especially from those areas which appeared different grossly and which were prepared according to standard methods. In the description which is to follow the structural changes as determined by hematoxylin and eosin, van Gieson and Weigert elastic tissue and fibrin stains will be treated as they occurred layer by layer. The bacteriology and mycology for which Levaditi, Ziehl-Neelsen and Giemsa stains were utilized will be reported separately following the complete description of the pathologic-anatomic alterations.

Mucosa.—At a distance from the margins of the ulcer, the mucosa appeared to be of average thickness and contained pits and tubules of normal appearance. In approaching an ulcer, the branched tubules gradually disappeared, leaving only crypts behind. Some of these were distended to form cystic swellings before the lining epithelium ended at the ulcer edge in a single horizontal layer of cells. The border of the mucosa was, as a rule, flush with that of an ulcer wall. The most noteworthy change in the mucosa was the presence of numerous lymphocytes, lymphoid and plasma cells, together with many macrophages and an occasional eosinophil, accumulated in the tunica propria. These cells were found in greatest numbers near the margins of the ulcer, but even at distant points they were present in abundance. For the most part, the infiltrate was a diffuse one, but here and there dense circumscribed collections resembling solitary nodules extended upward into the mucosa from the underlying layers.

Musculairis Mucosae.—The muscularis mucosae was, in all the sections examined, greatly thickened, especially in approaching the ulcers. At the border of an ulceration, the muscular tissue became thin and divided, and was obscured entirely by a cellular mass which formed the wall of the ulcer. Along with the thickening of the muscularis mucosae, which was due mainly to an increase in connective tissue, there was a separation and division of its substance into strands and bundles. Between the divided elements were accumulations of lymphocytes, lymphoid and plasma cells and macrophages. Extensions from these foci appeared to pass into the mucous layer. Here and there a large, circumscribed collection of cells projected from the submucosa through the muscularis mucosae to involve the mucosa. The included fibers of muscle were in such areas represented by few remnants of the original tissue. The vascular changes here were similar to those to be described in connection with the next layer.

Submucosa.—The submucosa was the seat of the most extensive and most marked changes. The thickening of the submucous layer, which under low magnification was its most conspicuous feature, was due to a diffuse production of granulation tissue associated with a chronic edema and the formation of dense inflammatory infiltrates. The involvement was present, not only in the immediate proximity of the ulcers, but also at a distance from them. The ulceration nowhere extended below the superficial portion of the submucosa. The floor of an ulcer was covered by fibrin, within the meshes of which were polymorphonuclear leukocytes and a cellular débris. Underlying the superficial fibrinous layer was a young granulation tissue rich in greatly dilated capillaries and cellular elements which consisted mainly of plasma cells. Beneath this layer of young granulation tissue were diffuse and circumscribed aggregates of cells in which the plasma variety overwhelmingly predominated.

The cellular infiltrates varied in size, circumscription and outline. In places the cells were thickly set, especially in the region of ulceration; in other places, they were rather widely separated by a loose, edematous granulation tissue. The well circumscribed accumulations of cytologic elements were for the most part round, and ranged from the size of a classic miliary tubercle to ten times that size. More or less diffuse, indefinitely demarcated, irregularly outlined collections of cells were found especially beneath the muscularis mucosae, penetrating into and separating its constituents into fractions and entering the mucosa. The intimate relationship of many of these aggregations to blood vessels was most conspicuous and will be discussed later. A striking feature was that the inflammatory infiltrates were, in almost all the sections examined, more prominent in the superficial one half of the submucosa. In the lower one half, the cellular elements tended to be perivascular in their distribution.

The cytologic elements comprising the submucosal aggregates were mainly lymphocytes, lymphoid and plasma cells in varying proportions, together with scattered macrophages and epithelioid cells. Some foci consisted entirely of closely packed lymphocytes, about which a few lymphoid and plasma cells were scattered. In others, the three types of cells were hereterogeneously mixed and present in approximately equal numbers. At the base of an ulceration, the plasma cells greatly outnumbered the other types. Most of the cellular collections had a more or less uniform, dark appearance, and contained a few capillary blood vessels and a barely visible reticulum. A few, however, and these were generally located just beneath the muscularis mucosae, presented a light area, usually central, made up of a structureless material separating the granuloma cells, which were well preserved. Giant cells such as are found in the muscularis propria were not present in the submucosal foci.

The perivascular grouping of the granulomatous cells (figs. 1, 2 and 3) was perhaps the most unique microscopic feature in the altered appearance of the submucosa. . The infiltrated cells formed bands of varying thickness, partial or complete, about many of the vessels. The small and medium sized vascular elements were affected to a greater degree than the larger blood vessels. The perivascular infiltrates consisted of the same type of cells found in the aggregates, which were unrelated to the vessels. In addition to the perivascular structures, the blood vessels themselves presented evidence of active participation in the inflammation (figs. 1, 2 and 3). A noteworthy fact was that the vascular involvement was peculiarly irregular in its distribution. One vessel may show extensive injury, a second a moderate degree of involvement and a third, located in an intermediate zone, may be entirely spared. This focal involvement was especially prominent in areas beyond the wall of the ulcer. The injury

to the vessels appeared to result mainly from granulomatous involvement similar to that found elsewhere. The invading elements were in some cases limited to the adventitia. In others, they extended to include the mediums and even the intima. Occasionally the intima, through multiplication of its lining cells, lead to narrowing or complete occlusion of a vessel lumen. In places, the combination of proliferation of the endothelial cells, granulomatous invasion and compression of the vessel was encountered (figs. 1, *a* and 2, *a*). Although the picture of recent and active panvasculitis was frequently noted, the number of totally obstructed vessels was very small. In not all cases was the entire circumference affected, for here and there a nodular swelling which projected from a portion of the wall of the vessel could be seen. Changes

Fig. 1.—Vascular and perivascular involvement in the submucosa. One vein (*a*) is totally occluded due to endothelial proliferation, panvasculitis and compression. In the other two veins (*b* and *c*) the granulomatous cells are limited mainly to the adventitia. The walls of the arterial elements (*d* and *e*) although encompassed by dense cellular aggregates are invaded to only a slight degree. Magnification, 100 diameters.

of a chronic nature indicated by the presence of an increase of adult fibrous tissue in one or more layers was uncommon.

A noteworthy and remarkable feature was the focal distribution of the vascular injury. Often a series of sections might disclose the fact that simply a segment of a vessel was involved, and what was particularly striking was that in cross-section merely a sector of that segment might be affected. Another distinctive character was that the veins bore the brunt of the injury accorded the vessels, for involvement of the arteries was far less marked. In

fact, the severe degree of phlebitis often contrasted strikingly with the mildness of the arteritis. In many fields in which an artery was relatively uninvolved, the accompanying vein or veins were greatly damaged. The reverse, however, was not true. When obliteration of an artery was encountered, which occurred only occasionally, the caliber of the affected vessel was usually quite small. Occlusion of the venous radicals, however, was not limited to the finer elements. The larger vessels were relatively free from granulomatous involvement.

Study of the vascular changes was greatly aided by preparations stained for elastic elements. In many vessels, the elastic ring appeared to be intact and normal. In some instances, the lamina elastica was frayed but unbroken.

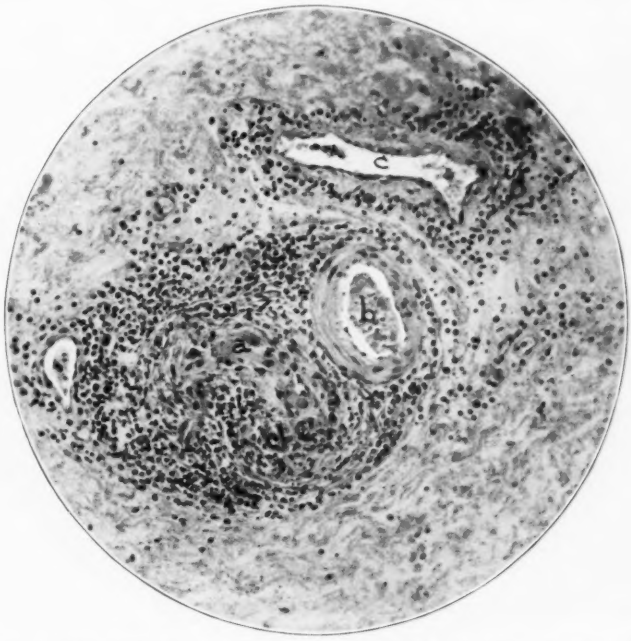

Fig. 2.—An area in the submucosa at a distance from figure 1. The endothelial proliferation and swelling, together with granulomatous invasion obliterates one vein (*a*). The wall and lumen of the accompanying artery (*b*) are unaffected. In a neighboring vein (*c*) the granulomatous elements are seen to extend from the adventitia to the mediums. Magnification, 125 diameters.

Excessive separation of the elastic elements was associated, as a rule, with a marked alteration in the normal architecture of the involved vessel. In some instances, otherwise indifferent structures were identified as vessels solely by the presence of retained elastic rings. On the other hand, some of the diffusely involved vessels, principally veins, recognized as such with the aid of counter-stains, had lost their elastic membranes entirely. Especially instructive were those pictures in which only a sector of a ring, corresponding to a localized granulomatous involvement of a vessel, had undergone elastolysis. The manner

in which vascular occlusion occurred was rendered clear in the sections stained by Weigert's method. The elastic membrane instead of practically bordering the lumen of a vessel was separated from the endothelial lining by constituents of the granuloma which encroached on the channel and produced a thickening of the wall of the vessel (fig. 3).

The Muscularis Propria.—This layer was also greatly altered, particularly in those areas in which the overlying submucosa showed high-grade changes. In that portion which was adjacent to the submucosa, there were found a slight thickening of the connective tissue and a marked increase of the elastic elements which normally occupied the boundary between the two coats. In the deeper

Fig. 3.—Endarteritis (*a*) and panphlebitis (*b*) (Weigert's elastin stain, counterstained with lithium carmine). In each vessel the elastic membrane is separated from the lining endothelium by granulation tissue which encroaches on the vascular channel. The eccentric situation of the lumen of the artery is the result of excessive thickening of a portion of the circumference of the intima. Magnification, 150 diameters.

layers, although vascular involvement was not lacking, it was not nearly as prominent as in the submucosa. The perineural lymphatics and tissues were the seats of cellular accumulations which closely resembled the perivascular infiltrates already described. Extension of the inflammatory cells between the neural elements was not infrequently encountered.

The degree of involvement and the type of alteration found in the muscularis propria varied in different sections examined. In some of the areas

investigated, edema of the intermuscular septums was found associated with rather sparsely infiltrated lymphocytes and lymphoid and plasma cells, the last predominating. In other places there were, in addition, moderate numbers of cells gathered in spaces of tissue, forming linear collections between bundles of muscles. In still other areas besides the rather diffuse infiltrates, there were dense cellular accumulations constituting smaller or larger circumscribed foci which invaded and replaced the normal substance of muscle (fig. 5). These foci were in the main round or oval, but here and there they were polymorphus. Some of the smaller foci were uniform, but the majority of these and practically all of the larger collections stained lighter in the central portions.

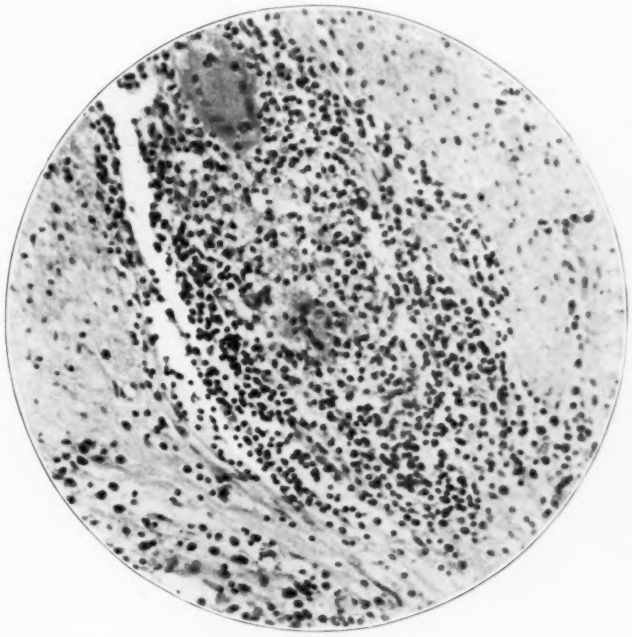

Fig. 4.—Miliary nodule located in a septum in the muscularis propria. Two multinucleated giant cells are present. Magnification, 225 diameters.

The circumscribed infiltrates which stained uniformly were composed of the same elements which constituted the submucosal aggregations. In the granulomatous foci with light centers (figs. 4 and 5) corresponding to these pale-staining areas, threads and granular débris separating widely the individual cellular elements of the infiltrate were found. The granulomatous cells were well preserved; their nuclei stained distinctly and did not exhibit regressive changes. The structureless material between the cells appeared to be derived from the pre-existent tissue in which the granulomas had developed. Thus, smooth fibers of muscle could be traced from the periphery of a granuloma to its center where the fibers became transformed into granules. In some of

the giant cells, a few of these granules, in addition to nuclear remnants, were engulfed. The central portions of these granulomatous foci consisted of lymphocytes, lymphoid, plasma and epithelioid cells, together with mononuclear macrophages and Langhans giant cells supported by a delicate granulation tissue in which a moderate number of capillaries were found. The arrangement of the cells comprising the light-staining centers were strikingly indefinite and irregular and lacked the precision of architecture seen for instance in miliary tubercles. The peripheral portions of foci with pale-staining centers consisted mainly of closely packed round cells. Multinucleate giant cells were not present in the outer zones of the granulomatous nodules.

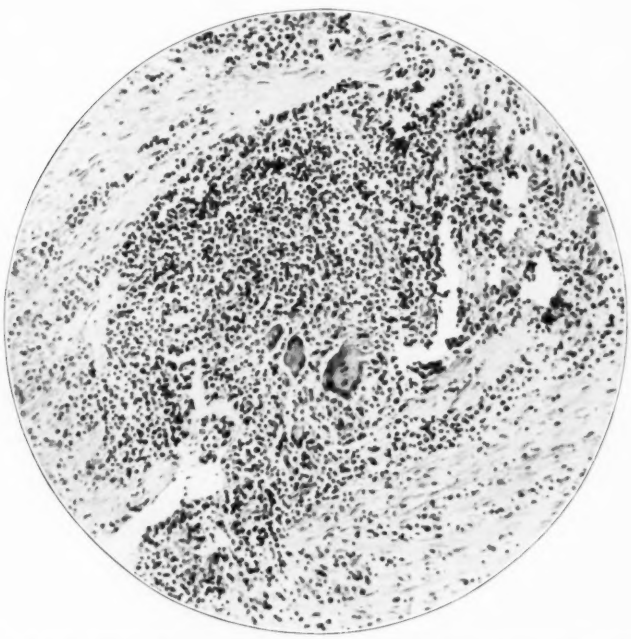

Fig. 5.—A miliary granuloma which has destroyed and replaced the original muscle fibers in the circular layer of the muscularis propria. In the region of the pale-staining granular débris there are four foreign-body giant cells. Magnification, 125 diameters.

Serosa.—The peritoneal covering was greatly thickened, and its normal elements were widely separated, owing to an edema fluid and the presence of numerous round cells together with a few macrophages. The infiltrate, which was diffuse, was more marked in some parts than in others, but nowhere was there any tendency toward dense accumulation or circumscription of the inflammatory cells. The vascular and perivascular involvement was noted in this layer also; however, not to the degree seen in the other coats.

Bacteriology and Mycology.—Specific stains for tubercle bacilli failed to disclose the presence of acid-fast organisms. In Levaditi preparations, in the

necrotic tissue forming the floor of an ulcer, were seen a number of spirochetes which had from four to eight coarse spirals resembling morphologically the spirilla of the mouth. These were found, on the whole, in association with fusiform bacilli and a number of other bacteria. Only occasionally could a spirochete invading intact tissue be identified beyond the fusospirochetal zone. Sections stained by the method of Giesma did not reveal any fungi.

SUMMARY AND COMMENT

At the time the case reported herewith came under observation (1925), we were led to believe that before the diagnosis of syphilis could be justifiably made the demonstration of either *Spirochaeta pallida* or the classic gumma was necessary. The experience of one of us (H. A. S.) with three subsequent cases in which the clinical, laboratory and anatomic observations pointed directly to syphilis of the stomach, but in none of which either of the foregoing requirements were fulfilled, led us to inquire into the frequency with which the spirochete of syphilis and the classic gumma were found in cases recorded in the literature as examples of gastric syphilis.

We were able to find but one report, that of McNee,[1] in which the demonstration of spirochetes in the gastric tissues led to its acceptance as one of proved acquired syphilis of the stomach. Critical analysis, however, proved to us that the organisms described and pictured were far more likely spirochetes of Vincent than *Spirochaeta pallida*. We therefore declined to accept McNee's diagnosis of the type of spirochetes present in his specimen, and concluded that in no case of acquired syphilis of the stomach has the spirochete of syphilis been satisfactorily demonstrated.

The most characteristic and, according to some authorities, specific lesion of syphilis is the fully developed (classic) gumma. It possesses an elastic (gummy) consistency apparently due to coagulative necrosis of a particular type. Other lesions found in syphilis, such as miliary gummas and dense cellular infiltrates, exhibiting a perivascular arrangement, are not as distinctive. Although present in other organs, such as the liver, lungs and spleen, classic gummas were entirely lacking in the stomachs of all the cases of syphilitis gastritis available for analysis.

Since we were unable to discover in the literature on acquired gastric syphilis any instance in which *Spirochaeta pallida* or the classic gumma was actually demonstrated, we concluded that either the diagnosis of syphilis of the stomach was erroneous in all the cases reported or else our criteria were too stringent. In not a small number of cases, although actual proof in the form of the specific organism or lesion of syphilis in the stomach was lacking, the evidence for gastric syphilis was so preponderant as to force us to conclude that our previous standards were inappropriate. As a result of our study, we learned that the nature of

an acquired syphilitic infection of the stomach was such as to lack actual proof of the condition, but it furnished a number of clinical, laboratory and anatomic characteristics which collectively justified the diagnosis.

We recalled our case of 1925, and reviewed it in the light of our revised impressions. As a result of this more recent study, we were disposed to consider the case as one of gastric syphilis and to submit the facts regarding it in some detail in order to give the reader an opportunity to weigh the evidence and to judge for himself. The clinical and laboratory characteristics of gastric syphilis are dealt with sufficiently in systems of medicine and in textbooks on diseases of the stomach to render a discussion here superfluous. The character of the anatomic changes in the stomach do not differ in any great essential from tertiary syphilitic lesions elsewhere, except, perhaps, that there is a greater tendency toward ulceration, which presumably is due to mechanical trauma and to the digestive action of the hydrochloric acid and pepsin when present.

SIMULTANEOUS NONSURGICAL DRAINAGE OF THE GALLBLADDER AND INTRAVENOUS CHOLECYSTOGRAPHY*

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There has been ample experimental proof of the ability to obtain bile from the gallbladder of animals, after certain substances have been instilled into the duodenum. Experimental evidence on man was first supplied by Silverman, and more recently by Lake and by Lyon and others. An extensive experience with duodenal bile drainage convinced us several years ago that a considerable amount of bile could be drained from the gallbladder by the method introduced by Lyon. In order to present further evidence of this fact, it was decided to carry out the following experiment. Twelve patients, whom we considered to be free from disease of the gallbladder, were studied. Each was given tetraiodophenolthalein intravenously at 9 p. m. after a fat meal of cream and milk had been ingested at 5:30 p. m. The gravity method was used. Three and five tenths grams of the dye dissolved in 100 cc. of physiologic sodium chloride were injected. Severe reactions did not occur. Five patients experienced slight nausea or dizziness for a short time after the injection. Pictures were taken at 9:45 the following morning. This work was carried out in the roentgen-ray laboratories of Dr. George Pfahler, at the Graduate Hospital.

The technic was uniform throughout the experiment. The plate target distance, central ray focus, factors of exposure, position of patient and development were identical in the examination of each patient. Immediately after this preliminary picture was exposed, a duodenal tube was passed. Three cases were discarded. In one, the gallbladder could not be visualized, and it was not possible to intubate the duodenum in two others. In the remaining nine cases, stimulating solutions were introduced into the duodenum, and subsequent x-ray exposures were made. Ninety cubic centimeters of a 33 per cent saturated solution of magnesium sulphate [1] was the first stimulating

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* Presented in the discussion of papers on the "Combined Studies of the Gallbladder by Nonsurgical Drainage and Roentgenography," by Dr. Lyon and Dr. Cole before the American Gastro-Enterological Association, May 1, 1928.

1. The percentage of magnesium sulphate solution throughout the discussion refers to "volumetric."

solution used in each instance. In all except two cases a second stimulant, 90 cc. of a 50 per cent solution of magnesium sulphate being used, was applied to the duodenum before the second cholecystogram was taken. In two of the nine cases, a 50 per cent solution of magnesium sulphate was again used, and a third cholecystogram was made. In three, a stimulation of 50 per cent solution of magnesium sulphate was followed by the intraduodenal instillation of 1 ounce of warm olive oil before the third cholecystogram. In the remaining four, olive oil alone was used after the second cholecystogram, and a third cholecystogram was taken as soon as a satisfactory drainage of bile occurred. Immediately

Results of Experiments of Obtaining Bile from the Gallbladder by Stimulation of the Duodenum *

	X-Ray, Film 1		X-Ray, Film 2				X-Ray, Film 3				X-Ray, Film 4 (After Fat)	
Name	Size, Mm.	Density	Stimulant	Bile, Cc.	Size, Mm.	Density	Stimulant	Bile, Cc.	Size, Mm.	Density	Size, Mm.	Density
J. H.	70-33	1	33	32 N.B.	74-33	1	0.0	65 M.B.	58-19	1	Not visual	
D. K.	53-26	4	33	50 Y.			50	0				
			50	80 L.B.	41-22	3	0.0	24 M.B.	28-10	±	Not visual	
L. S.	56-25	3	33	0			0.0	30 Y.	41-26	±	30-16	1
			50	20 L.B.	41-25	2						
F. B.	92-35	4	33	25 L.B.			0.0	60 D.M.B.	66-24	2	75-29	3
			50	50 O.B.	80-34	3						
T. D.	56-21	3	33	30 M.B.	41-29	3	50	0				
							0.0	40 M.B.	36-27	2	36-15	1
B. C.	70-23	4	33	60 Y.			50	33 M.B.	50-18	2	44-10	2+
			50	70 M.B.	58-22	3						
A. J.	61-19	4	33	50 M.B.			50	55 M.B.	22-10	3	10- 5	3
			50	32 L.B.	31-17	4						
S. W.	83-45	3	33	22 M.B.			0.0	20 D.O.G.	57-18	±	59-20	±
			50	77 M.B.	68-24	2						
H. M.	69-28	1	33	70 B.	65-42	1	50	60 Or.			42-18	2+
							0.0	10 B.	50-24	2		

Size: first column is the greatest length and second the greatest width. Density: grades 1, 2, 3 and 4. Stimulant: stimulating solution introduced into the duodenum; 33 = 33.3, and 50 represents volumetric percentage of magnesium sulphate solution; 0.0 = 30 cc. of olive oil. Bile (cc.): letters refer to color of bile obtained: N.B. indicates normal brown; Y., yellow; L.B., light brown; O.B., orange brown; M.B., mahogany brown; B., brown; D.M.B., dark mahogany brown; D.O.G., dark olive green; Or., orange.

following the third cholecystogram, the duodenal tube was removed and a fat meal, consisting of a glass of equal parts of milk and cream and one raw egg, was administered by mouth. One hour later, a fourth cholecystogram was made. The first cholecystogram on the first patient was taken at 9:30 a. m., and the last exposure on the last patient was completed at 4 p. m. The total time taken for the experiment including pictures before the tubing, duodenal intubation with drainage, subsequent exposures of the gallbladder and the administration of the fat meal with cholecystograms one hour later was six hours and twenty-five minutes. The results of this experiment are statistically recorded in the accompanying table, and graphically illustrated by one case (A. J.).

In the first column of the table is the measurement of the length and width of the gallbladder shadow as depicted by the first cholecystogram. In the second is the grade of density of the gallbladder shadow. The figure in the next colum represents the percentage of magnesium sulphate solution used. This is followed by the amount and color of bile

Fig. 1.—Cholecystogram of A. J. before stimulation. The gallbladder shadow is 61 by 19 mm. The density grade is 4.

obtained. The size and density of the gallbladder shadows after stimulation are then recorded (x-ray film 2). In all except two cases following this first series of stimulations with magnesium sulphate, the size of the gallbladder shadow had definitely decreased. The gallbladder in these two cases (J. H. and H. M.) was only faintly visualized before drainage,

and only one stimulant of 33 per cent magnesium sulphate was used. A decrease in the density of the gallbladder shadow occurred in five of the nine cases following stimulation with magnesium sulphate. We may conclude from the comparative study of the x-ray films before and after stimulation with magnesium sulphate that: (1) intraduodenal instilla-

Fig. 2.—Cholecystogram of the duodenal tube of A. J.; showing marked reduction in size after two instillations of magnesium sulphate. The gallbladder shadow is 31 by 17 mm.; the density grade 4.

tion of magnesium sulphate causes a prompt reduction in the size and usually in the density of normal gallbladders, and (2) a 50 per cent solution induces a better evacuation of the contents of the gallbladder than a 33 per cent solution.

SECOND SERIES OF STIMULATING SOLUTIONS

In cases B. C., and A. J., 50 per cent of a saturated magnesium sulphate solution was repeated, and further reduction in both the size and the density of the shadow of the gallbladder was accomplished (x-ray film 3). A repetition of the magnesium sulphate stimulant in cases

Fig. 3.—Cholecystogram of A. J., showing marked reduction in size after the instillation of a 50 per cent solution of magnesium sulphate. The gallbladder shadow is 22 by 10 mm.; the density grade 3.

D. K. and T. D. did not cause any further appearance of a "B" fraction. Olive oil was then used, and that there was further reduction in both size and density of the shadow is evident from x-ray film 3. In case H. M., 60 cc. of orange bile (some "B" fraction) followed the use of

magnesium sulphate, and the intraduodenal instillation of olive oil caused an evacuation of only 10 cc. of brown bile; in spite of this scant flow of "B" bile, the gallbladder was considerably reduced in size on x-ray film 3. In the second series of stimulations, olive oil alone was applied to the duodenum in four cases. In all except one

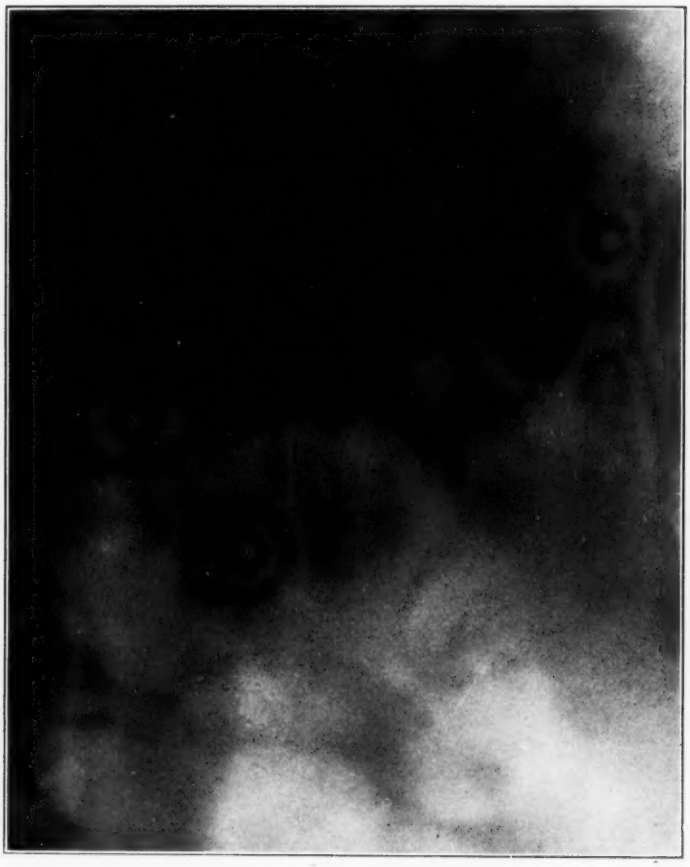

Fig. 4.—Cholecystogram showing still further reduction after a fat meal. The shadow is 10 by 5 mm.; the density is the same as that of figure 3.

case, the third x-ray film showed a further reduction in the size of the gallbladder as compared to the x-ray films taken after stimulation with magnesium sulphate. In the exceptional case (L. S.), the density of the gallbladder was so reduced as to be scarcely visible. In every

case except this one, the second series of duodenal instillations caused a further reduction in the size of the gallbladder. Since this shadow was markedly reduced in density and maintained the same size, it is obvious that the stimulating solution caused further evacuation of the contents of the gallbladder in every case. The density was decreased in all cases except J. H. and H. M.; these cases were only faintly visualized at the start (possibly diseased gallbladders). In case S. W., the gallbladder was large, well-visualized and filled with stones. Nevertheless, it was markedly reduced in size by drainage and the outline became faint after two stimulations with magnesium sulphate and one with olive oil. A study of the bile and cholecystograms, after a second series of stimulating solutions applied to the duodenum, reveals the following: 1. The gallbladder can be further reduced in size after a second or third stimulating solution is used. 2. The failure to obtain a dark fraction of bile on one occasion does not necessarily mean that the gallbladder has not partially emptied its contents. It seems probable that in some cases a considerable amount of the bile which enters the duodenum passes on down into the intestines. In most instances, however, the amount of "B" bile recovered seems commensurate with the reduction in the size and density of the gallbladder shadow. 3. Olive oil is slightly more efficient as a stimulant to the flow of bile from the gallbladder than magnesium sulphate. 4. The gallbladder was not completely emptied after intraduodenal instillation of magnesium sulphate or olive oil in any case. 5. Considering both the size and the density of the shadow, the emptying of the gallbladder after bile drainage was greater than one half its contents in seven of nine cases. The remaining patients may have had diseased gallbladders, as the original shadow was faint.

An interesting comparison is that between the third x-ray film taken after bile drainage had been completed, and the fourth taken one hour after a fat meal. It will be noted that in two cases (F. B. and S. W.) further reduction in size or density of the gallbladder shadow was not accomplished by a fat meal. In fact, the shadow was slightly larger in both cases. Of the remaining seven cases, the gallbladder shadow after the fat meal was smaller in five and had disappeared entirely in two. On the whole, the reduction after a fat meal was not as great as we had anticipated. If it is fair to judge from this small series of cases, about 30 per cent of gallbladders will be emptied as well by the duodenal tube method as by an oral fat meal. This may not represent a true percentage, as the fat meal was used after the gallbladders had been markedly reduced in size as a result of biliary drainage. In four cases, the density of the gallbladder was greater, and in two cases it was the same as the density of the shadow before the fat meal. The explanation for this is not clear.

CONCLUSION

Simultaneous duodenal bile drainage and cholecystography were carried out in nine cases. A marked reduction in the size of the gallbladder shadow occurred after medical bile drainage in every case. A decrease in the density occurred in all except two cases; one of these did not become less dense after a fat meal. The stimulants used in the duodenum were 33 and 50 per cent solution of magnesium sulphate and olive oil. Their effectiveness as gallbladder evacuants is about in the order given, the 33 per cent solution of magnesium sulphate being least effective and the olive oil most effective. The gallbladder was not completely emptied by this method in any case. Taking into consideration the size and density of the shadow, in seven cases the emptying was more than one-half. At the completion of bile drainage, the administration of a fat meal by mouth brought about further evacuation of the contents of the gallbladder in seven of nine cases. No further change occurred in two of the cases. The amount of "B" bile recovered after stimulation was commensurate with the reduction in the size and decrease in density of the gallbladder shadow in most instances. We estimate that medical bile drainage properly conducted will evacuate the gallbladder as well as a fat meal by mouth in 30 per cent of cases and that it will cause an appreciable drainage of bile from a normal gallbladder in practically every case.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

III. AGE FACTOR IN THE PRODUCTION OF BRADYCARDIA*

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Since Röhrig's [1] fundamental work, which was based on the observance of a slow pulse in jaundice, the reaction of the heart to bile has been the subject of numerous investigations. Acute experimental work with the biliary constituents has constituted the bulk of research on the cardiovascular effects of bile. Important as such contributions may be, the effects produced by suddenly crowding into the circulating blood certain of the bile constituents, and that of gradual absorption into the blood and tissues of these and other products following obstruction to the flow of bile in its channels may not be identical, although the patterns of response in either case, particularly with reference to the bradycardia, may in some way be similar.

METHODS

This study extended over a period of two years. Five litters of puppies, a part of a sixth litter and six adult dogs, in all thirty-five animals, were studied, observations being made on only one litter at a time. The puppies were between 4 and 7 weeks old at the start of the experiments. The adult animals were healthy and free from mange. Jaundice was produced in the animals by ligation and division of the common bile ducts under ether anesthesia. In all but one litter, several mates on which operation was not performed served as controls.

The heart rate of the animals was taken twice a day with a Bowle's stethoscope placed over the precordium. Control rates were observed over a period of between five and fifteen days. This procedure was adopted in two litters throughout the obstructive jaundice and up to the time of the animals' death, and in the others for not more than fifteen or twenty days after the ligation and division of the common bile duct, when they were used in other experiments. A uniform method of taking the pulses was adopted. The pulse was counted only after the animals lay reasonably quiet in the lap for a minute or two. It was taken about one hour after each of the two meals, in the morning and in the afternoon. The pulse rates were counted from the second hand of a watch. Repetition of the performance gave a more than fair degree of accuracy.

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* This work was conducted in part under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

* Read before the American Physiological Society, Ann Arbor, Mich., April 13, 1928.

1. Röhrig, A.: Ueber den Einfluss der Galle auf die Hertz Tätigkeit, Arch. d. Heilk. **4**:385, 1865.

Electrocardiograms were made of the puppies from three of the litters before and after jaundice was produced. In one litter they were made almost daily for the first ten or twelve days following obstruction; subsequently, the interval varied between three and ten days. In the second litter, the intervals between tracings were from three to twenty days. The effects of atropine were noted in a third litter.

Blood calcium determiaitons[2] were made on all the puppies at ten to fourteen day intervals. The weight of the animals were recorded every three days.

Twice a day, the animals were given a well balanced diet consisting chiefly of meat, bread, dog biscuit, cooked vegetables and milk. Two litters were kept in 3-foot square cages. The other puppies were allowed to run free in a room. The animals that developed mange or apparent postoperative infections were excluded from the series.

In another group of experiments on decerebrated frogs, simultaneous kymographic and electrocardiographic tracings were made of the suspended heart, in which were noted the effects of the sudden release of bile from the gallbladder after its incision. As bile did not prove to be an acute peritoneal irritant to the frog, it was usually allowed to spill into the peritoneum. In another set of experiments, the common bile duct of the frog was ligated and divided under ether anesthesia, and the abdominal wall was subsequently sewed up. From one to ten days later after the animal was decerebrated, kymographic tracings were made of the suspended heart. The hooked projections of an ordinary burr were used to attach the heart to the lever.

RESULTS

A marked slowing of the heart action occurred in all the puppies soon after jaundice was produced by ligation and division of the common bile duct. By the second or third day, in almost every instance, the heart rate was slowed between thirty and fifty beats or more per minute Bradycardia in the adult jaundiced animal, however, was not encountered in any instance.

In the puppy, the most acute slowing of the heart rate usually occurred during the first five days after obstruction. The pulse rate became progressively slower from this time to the twentieth or thirtieth day, when it usually reached its lowermost level. After this, there was an acceleration of the heart, the acuteness of which almost paralleled that of the slowing seen in the initial stage of the obstruction. In the plotted curve (fig. 1) of the mean pulse rate, a series of rather acute rising peaks, with a tendency toward increased heart rate, are noted immediately following the initial bradycardia. This period I have designated as one of relative tachycardia, although the heart rates were considerably slower than those of the nonjaundiced control litter mates. It extended roughly from the twentieth to the sixtieth day of obstruction. Afterward the heart rate of the icteric animal overtook that of the control litter mate, on which operation was not performed; the rate

2. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serums and Plasma, Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921.

of the control animal had become slower as the result of age and growth. Throughout the remaining period of obstruction, the heart of the jaundiced animal, although it tended to become somewhat slower, continued to beat more rapidly than that of the nonjaundiced one. The last period was, therefore, designated one of absolute tachycardia.

The trend of the heart rate of puppies subjected to ligation and division of the common bile duct was such, therefore, as may be conveniently divided into three periods: (1) one of a marked initial bradycardia, (2) that of relative tachycardia and (3) that of an absolute tachycardia.

During the first ten days or more of obstruction, the activity of the animal operated on was but slightly diminished as compared to that

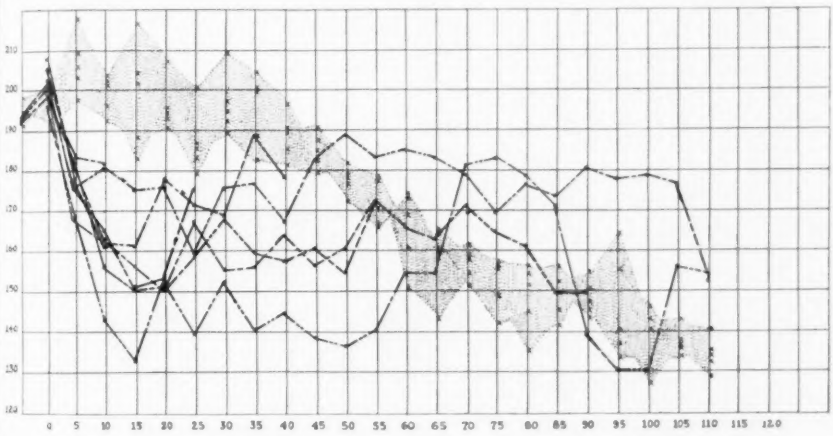

Fig. 1.—Plotted curve showing the characteristic trend of the heart rate of puppies subjected to ligation and division of the common bile ducts. The shaded area represents the trend of the heart rate of the nonjaundiced control litter mates. The ordinates represent heart rate; the abscissas, days after the induction of jaundice.

of the control litter mate on which operation was not performed. For this short period, it seemed none the worse off. Following this, there was a progressive decline in its vigor and strength; it was less active, less playful and possibly more combative than its control litter mate. Marked nutritional disturbances were evident, and the animal became pot-bellied or developed an ascites. Slight dyspnea was usually present during this second period in which a relative tachycardia was noted. During the third period of obstruction, and at the time an absolute tachycardia was present, the animal revealed cretinoid or rachitic characters, showed a central depression and eventually become cachectic.

Daily Heart Rates of the Jaundiced Puppies and Control Litter-Mates During the First Seventy Days of Obstruction *

	Litter I							Litter II						
	Preoperative Control Period					Nonjaundiced Control Litter Mates		Preoperative Control Period				Nonjaundiced Control Litter Mates		
	206	212	200	190	188	204	224	202	186	193	190	190	191	
	178	206	206	214	196	196	216	196	182	190	204	200	210	
	202	210	196	230	206	220	226	204	192	200	198	186	190	
	185	190	176	206	208	210	210	200	198	200	200	192	200	
	208	196	192	210	218	230	224	194	186	202	186	186	192	
	206	210	198	196	204	200	214	196	200	200	190	178	196	
	195	204	196	184	212	196	204	220	224	214	222	200	208	
	190	208	192	188	196	206	212	202	200	212	198	210	204	
	Ligation and Division of Common Bile Duct							Ligation and Division of Common Bile Duct						
Days														
2	198	226	188	212	194	206	192	190	190	182	184	194	208	
	198	204	190	186	198	200	192	176	232	170	228	204	224	
3	190	180	182	184	170	230	210	172	176	166	184	184	220	
	162	168	200	170	170	194	174	166	176	158	204	202	222	
4	178	186	190	182	184	220	204	180	170	162	210	220	232	
	166	168	164	196	180	192	192	170	188	142	214	222	206	
5	156	190	180	142	176	200	200	178	178	180	214	202	228	
	140	164	168	158	180	206	202	180	156	168	208	206	210	
6	138	170	178	152	154	218	198	176	180	176	202	200	218	
	152	158	180	164	166	220	208	168	190	166	204	203	220	
7	134	178	160	138	170	212	190	186	168	180	208	224	212	
	144	180	154	162	170	228	194	170	172	168	204	212	208	
8	130	154	156	168	154	216	180	196	178	174	226	226	220	
	142	152	148	180	170	218	210	172	170	166	208	208	194	
9	170	162	160	182	156	206	220	196	142	158	174	194	164	
	180	146	160	176	164	186	220	216	172	170	218	204	210	
10	144	174	162	164	172	184	190	162	204	126	142	184	182	
	136	184	150	172	180	190	178	192	186	170	208	204	190	
11	140	140	162	152	150	180	180	160	182	164	186	188	216	
	146	158	150	156	140	192	168	168	250	152	190	180	240	
12	146	136	150	146	240	204	165	196	214	176	224	210	222	
	160	166	144	178	...	180	180	168	...	160	200	180	202	
13	130	164	154	146	...	198	192	188	...	152	198	198	224	
	140	160	142	162	...	200	202	190	...	160	200	194	206	
14	129	160	144	138	...	170	202	178	...	160	206	198	218	
	124	180	164	126	...	186	200	200	...	176	220	216	226	
15	114	134	168	148	...	173	168	180	...	178	212	212	240	
	128	150	130	162	...	190	212	148	...	154	182	188	200	
16	126	132	150	140	...	208	150	170	...	150	210	232	230	
	140	180	152	150	...	218	204	142	. .	154	184	188	206	
17	150	142	156	158	...	200	204	202	...	198	232	216	232	
	152	164	160	154	...	220	194	160	...	198	208	200	200	
18	118	150	164	124	...	186	156	160	...	160	184	186	200	
	124	160	132	160	...	186	178	170	...	158	176	190	208	
19	180	124	150	132	...	180	170	172	...	152	190	200	200	
	168	160	154	164	...	192	190	194	...	170	186	200	222	
20	180	146	146	162	...	212	194	180	...	182	186	200	222	
	162	150	140	144	...	190	204	182	...	180	194	182	200	
21	144	160	164	150	...	198	192	172	...	178	184	182	200	
	140	154	152	176	...	186	114	180	...	194	196	172	188	
22	126	166	160	150	...	164	170	170	...	202	208	180	208	
	138	168	176	160	...	170	190	180	...	190	190	188	210	
23	146	146	168	162	...	200	210	142	...	166	166	190	202	
	148	156	156	160	...	190	212	172	...	170	172	206	190	
24	134	134	164	138	...	196	184	142	...	156	184	180	190	
	146	160	170	156	...	142	180	172	...	184	214	196	220	
25	154	156	160	172	...	180	182	120	...	126	160	160	180	
	150	154	172	180	...	200	200	152	...	166	198	210	212	
26	114	172	180	164	...	174	150	172	...	168	192	190	214	
	130	164	160	160	...	170	170	166	...	190	146	160	194	
27	154	178	170	158	...	206	200	182	...	164	194	210	218	
	144	166	160	160	...	208	198	182	...	162	198	190	202	
28	150	164	168	...	...	180	194	184	...	172	208	200	240	
	170	170	140	...	...	182	180	162	...	160	200	208	192	
29	182	164	174	...	...	214	174	158	...	160	188	206	206	
	170	170	144	...	...	206	198	174	...	150	158	174	190	
30	156	164	162	...	...	186	190	170	...	168	180	176	232	
	156	164	138	...	...	176	186	196	...	176	200	218	206	
31	148	164	132	...	...	190	194	184	...	174	186	190	200	
	158	164	160	...	...	200	186	170	...	190	210	200	202	
32	152	162	166	...	...	200	180	156	...	180	188	190	192	
	156	156	140	...	...	204	190	166	...	184	206	200	188	
33	130	160	152	...	...	216	184	180	...	170	200	216	212	
	140	158	144	...	...	188	192	160	...	198	210	192	214	

* The rates were obtained with a stethoscope placed over the precordium.

Daily Heart Rates of the Jaundiced Puppies and Control Litter-Mates During the First Seventy Days of Observation—Continued

	Litter I							Litter II						
	Preoperative Control Period					Nonjaundiced Control Litter	Mates	Preoperative Control Period				Nonjaundiced Control Litter		Mates
34	144	152	142	...	...	216	196	152	...	168		200	190	200
	128	152	150	...	...	180	178	170	...	170		188	190	190
35	128	172	172	...	...	208	172	204	...	180		208	218	216
	136	152	160	...	...	210	190	200	...	200		190	200	202
36	154	170	174	...	...	176	174	196	...	218		200	212	224
	132	160	158	...	..	180	170	190	...	220		198	194	204
37	144	156	170	...	...	182	168	150	...	182		202	200	222
	150	158	158	...	...	200	196	172	...	166		176	184	178
38	142	143	162	...	...	184	182	166	...	192		196	186	192
	134	162	168	...	...	200	188	170	...	180		200	188	198
39	140	132	172	...	...	160	170	170	..	178		200	190	218
	150	174	204	...	...	180	200	144	...	152		150	144	164
40	138	168	160	...	...	184	166	178	...	176		190	180	192
	150	158	146	...	...	170	164	170	...	168		184	202	206
41	152	156	138	...	...	200	196	174	...	186		180	190	186
	146	166	148	...	...	190	185	174	...	186		208	186	202
42	138	174	152	...	...	218	184	176	...	172		190	192	196
	138	168	166	...	...	194	190	152	...	164		192	180	194
43	138	158	150	...	...	190	180	180	...	..		194	176	176
	160	178	156	...	...	204	162	196	...	...		190	174	190
44	128	160	156	...	...	180	192	150	...	...		204	196	186
	146	168	178	...	...	200	184	172	...	...		186	180	182
45	138	158	184	...	...	162	188	186	...	...		180	186	182
	134	162	150	...	...	164	192	192	...	...		180	172	194
46	138	136	142	...	...	180	182	212	...	...		194	186	190
	148	128	164	...	...	192	174	198	...	...		184	184	186
47	148	128	164	...	...	192	174	176	...	...		184	184	186
	130	132	150	...	...	168	162	202	...	...		186	178	192
48	138	156	152	...	...	182	180	192	...	...		184	168	188
	132	170	144	...	...	200	182	190	...	...		188	174	174
49	140	170	174	...	...	166	150	194	...	...		184	170	192
	128	160	166	...	...	200	192	194	...	...		184	176	180
50	122	160	158	...	...	144	186	186	...	...		176	170	188
	130	138	172	...	...	166	186	168	...	...		176	170	160
51	132	180	156	...	...	172	180	190	...	...		156	164	166
	160	150	166	...	...	206	198	168	...	...		158	166	166
52	112	150	176	...	...	182	192	170	...	...		168	160	172
	132	152	186	...	...	176	184	190	...	...		178	170	164
53	140	182	190	...	...	180	190	182	...	...		142	146	160
	136	168	172	...	...	178	186	186	...	...		168	172	178
54	136	156	174	...	...	186	152	180	...	..		174	179	198
	144	154	166	...	...	190	172	182	...	...		158	148	162
55	140	162	168	...	...	172	156	186	...	...		166	158	156
	138	188	174	...	...	176	172	172	...	...		168	166	176
56	162	188	170	...	...	170	186	194	...	...		168	176	162
	164	208	144	...	...	174	190	198	...	...		170	172	168
57	132	206	154	...	...	159	168	178	...	...		170	174	170
	140	178	160	...	...	170	180	176	...	...		164	168	176
58	172	140	158	...	...	132	164	176	...	...		180	174	160
	172	112	160	...	...	162	154	176	...	...		170	176	174
59	134	...	170	...	...	160	180	176	...	...		192	180	176
	158	...	186	...	...	150	158	174	...	...		180	176	168
60	162	...	186	...	...	124	146	200	...	...		168	182	174
	164	...	180	...	...	160	158	200	...	...		168	178	160
61	166	...	160	...	...	128	140	200	...	...		172	164	172
	142	...	144	...	...	134	156	190	...	...		162	164	174
62	186	...	140	...	...	144	164	156	...	...		144	142	156
	164	...	152	...	...	146	162	176	...	...		160	152	158
63	138	...	150	...	...	148	166	186	...	...		156	160	154
	132	...	168	...	...	122	148	178	...	...		162	170	162
64	162	...	156	...	...	132	150	190	...	...		168	170	162
	146	...	170	...	...	138	170	206	...	...		160	168	164
65	150	...	164	...	..	138	158	182	...	...		168	166	154
	150	...	182	...	...	164	166	186	...	...		162	180	162
66	166	...	170	...	...	150	154	182	...	...		178	172	182
	150	...	180	...	...	154	150	186	...	...		180	174	158
67	166	...	200	...	...	150	146	186	...	...		170	158	170
	180	...	164	...	...	162	170	182	...	...		138	146	158
68	190	...	168	...	...	136	144	178	...	...		146	168	162
	176	...	144	...	...	150	162	160	...	...		154	160	160
69	180	...	150	...	...	174	150	192	...	...		154	166	162
	176	...	178	...	...	162	156	186	...	...		160	158	162
70	192	...	180	...	...	156	154	188	...	...		146	166	166
	182	...	174	...	...	150	152	170	...	...		156	154	162

Its appetite, however, often remained quite voracious although there were short intervals of marked anorexia. Marked dyspnea was present, even in the absence of effusions into the peritoneum, although these effusions may aggravate this symptom.

Respiratory variations of the heart rate were present in the normal puppy when the heart was not beating excessively fast. The electrocardiogram revealed their presence at rates of 200 or more per minute. When the heart rate was 170 or less, it was usually detected with ease by the auscultatory method. All manner of stimuli, slight movements of the body and slight respiratory irregularities occasioned abrupt transitions in the heart rate of the normal puppy. It sometimes suddenly advanced from 150 to 250 beats per minute. Readjustment with removal of the stimulus, whatever it might be, was quick. The heart was exceptionally labile and responsive. Marked activity on the part of the jaundiced puppy during the first period of obstruction was also followed by an increase in the heart rate that approximated that observed for the nonjaundiced animal. The tachycardia was usually not so marked, and it is my impression that the transition was not so rapid. Since bradycardia was established at the time of the obstruction, the differences between the minimal and maximal heart rates were, therefore, greater in the jaundiced animal. Slight respiratory irregularities in this animal did not so readily upset the established rhythm of the heart, and despite the wider range over which the heart rate of the jaundiced pup might vary in the initial obstructive period, a tendency toward fixation of the rate was noted. After thirty days or more of obstruction, the infrequency with which respiratory variations of the heart occurred, so readily noted in the animals on which operation was not performed, became more noticeable. In the later periods of obstruction, the observation of a comparatively much more regular heart and of a rhythm much less influenced by respiration was even more evident.

Gross irregularities of the heart were not detected at any time during the period of obstructive jaundice, nor did the electrocardiograph reveal them.

A study of the heart rate of the adult animal revealed the absence of slowing at any time during the obstruction. A slight acceleration of the pulse rate was usually present. The animal lived a relatively much shorter time after the induction of jaundice, the tissues became more deeply bile stained and the intoxication seemed more severe. While ascites was a common complication it occurred earlier, and autopsy disclosed it almost invariably associated with a perihepatitis and a chronic exudative peritonitis, of which the animal usually died. In spite of the marked ascites often encountered, the symptoms of dyspnea were inconspicuous or absent. The usual respiratory variations of the heart were present at all times, and they did not appear to be exaggerated.

Five minutes after atropine (1 mg. per kilogram of body weight) was administered to the jaundiced and nonjaundiced litter mates, and at a time when a bradycardia was established, practically maximum heart rates (from 280 to 300) were obtained in both groups. The highest rate was noted in one of the jaundiced animals.

The blood serum calcium in puppies with obstructive jaundice fell progressively to about two-thirds the normal values before death.[3]

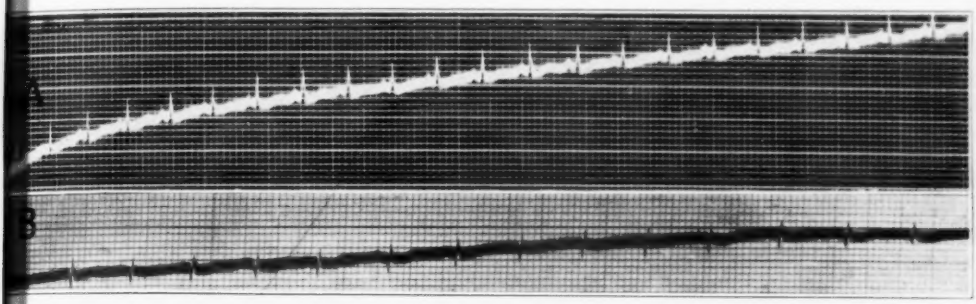

Fig. 2.—*A*, control curve; lead I; rate 210. *B*, curve made four days after obstruction; lead I; rate 145; voltage. Right predominance and slight sinus arrhythmia.

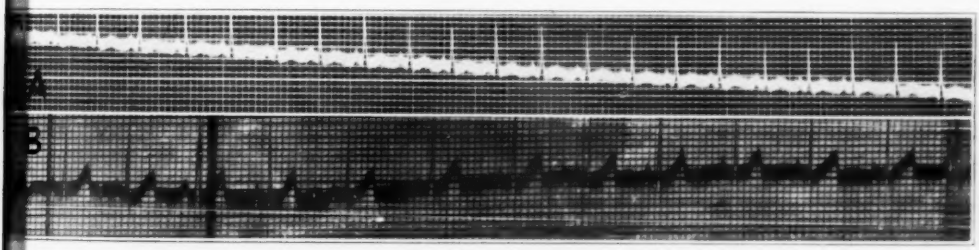

Fig. 3.—*A*, control curve; lead I; rate 217. *B*, curve made thirteen days after obstruction; lead I; rate 140. sinus arrhythmia.

THE ELECTROCARDIOGRAM

Typical examples of slowing of the heart rate are seen in figures 2 and 3.

The most frequent abnormality encountered in the electrocardiograms of two litters of puppies comprising eleven animals was an inversion of the T-wave (fig. 4). The two control animals showed a transient negativity in the first and third leads, respectively. Of the nine animals

3. Buchbinder, W. C., and Kern, Ruth R.: Experimental Obstructive Jaundice: I. Growth Factor in Defective Calcification, Arch. Int. Med. **40**:900 (Dec.) 1927.

in which jaundice was produced, six developed negativity, although the T-wave had been upright in all the control tracings except one in which it was diphasic in the first lead. In two animals, the T-wave became inverted in all leads; in another, negativity was displayed in the second and third leads. The fourth animal which had a diphasic T-wave in the first lead of the control tracing developed an inversion in this lead with diphasic T-waves in the second and third leads. The remaining two puppies of the operated series developed a T-wave negativity in the

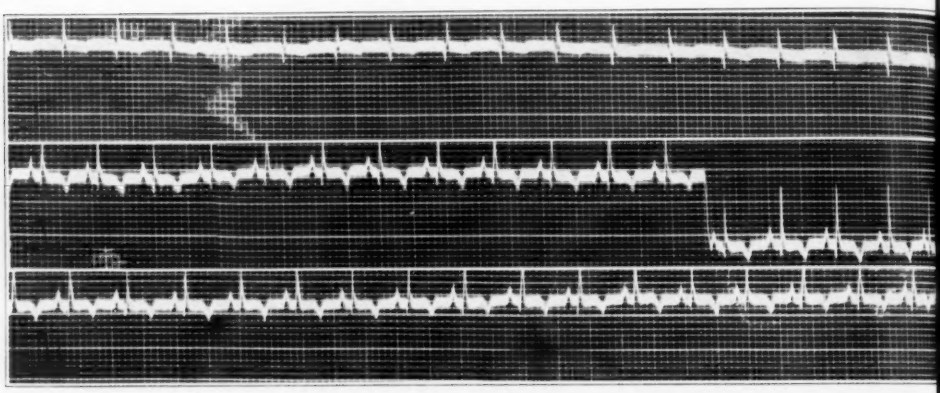

Fig. 4.—Curve made 108 days after ligation and division of the common bile duct, showing inversion o T-wave wall ledges. Average rate in all leads, 171. There is not any variation in the PR interval in lea and III; in lead I it is 0.01 seconds.

Fig. 5.—Curve taken ten days after the induction of jaundice, showing a transient dislocation of the pace-m

first and third leads, respectively. The two control dogs in which jaundice was produced after their litter mates were dead also developed a negativity in the first and third leads, respectively, although the T-wave had been upright during the 100 days or more during which they served as controls. The latter were studied for but a short time after the induction of jaundice. Including the three animals in which a diphasic T-wave was noted in one of the leads, negativity was observed in eight of the eleven puppies subjected to ligation and division of the common bile duct.

The time at which negativity was disclosed after this operation was variable, and ranged between the third and sixty-fifth day. Two points, however, are worthy of mention: (1) Negativity was transient in most cases and it was not a permanent feature for any length of time except in a few instances. Even in those instances in which it may have been noted in several successive tracings, at the time of death the T-wave was upright. (2) T-wave negativity developed early (in from three to ten days) after the ligation and division of the common bile duct in nearly half the number of animals studied electrocardiographically, and at some time prior to that when they evidenced cardiac embarrassment and damage, in the tachycardia, dyspnea and muffling of the heart tones.

The electrocardiogram does not reveal in any instance a prolongation of the PR interval. Aberrant QRS complexes were not observed, and the time occupied by them was not lengthened. Transient dislocation of the pacemaker was encountered in one animal ten days after the induction of jaundice (fig. 5). Although more than half the number of jaundiced puppies developed ascites, transient right ventricular preponderance was found in only one instance.

REFLEXES FROM THE GALLBLADDER TO THE HEART IN THE FROG

Incision into and release of bile from the gallbladder of the decerebrated frog produced almost invariably a sudden marked slowing of the heart rate, with a markedly increased force of the beats. It was possible to prolong this action over a period of fifteen minutes or more, before the normal rhythm was reestablished. Typical reflexes following this operation are shown in figure 6. Destruction of the medulla, decapitation or atropinization prevented the reflex or abolished it at once. Simultaneous electrocardiographic and kymographic tracings revealed some striking changes. Apart from the marked slowing due to sinus block (fig. 7) a sudden inversion of the T-wave was frequently seen (fig. 8). Acute distention of the gallbladder or cannulated common bile duct also produced a similar reflex, but usually of shorter duration. Marked distention of the gallbladder occurred in frogs which had had their common ducts ligated and divided for several days. In these frogs, spontaneous arrhythmias and sudden halving of the rate were frequently observed.

COMMENT

There has been a common understanding for many decades that a slow pulse rate is one of the usual accompaniments of obstructive jaundice, and in most modern textbooks of medicine one finds much, and

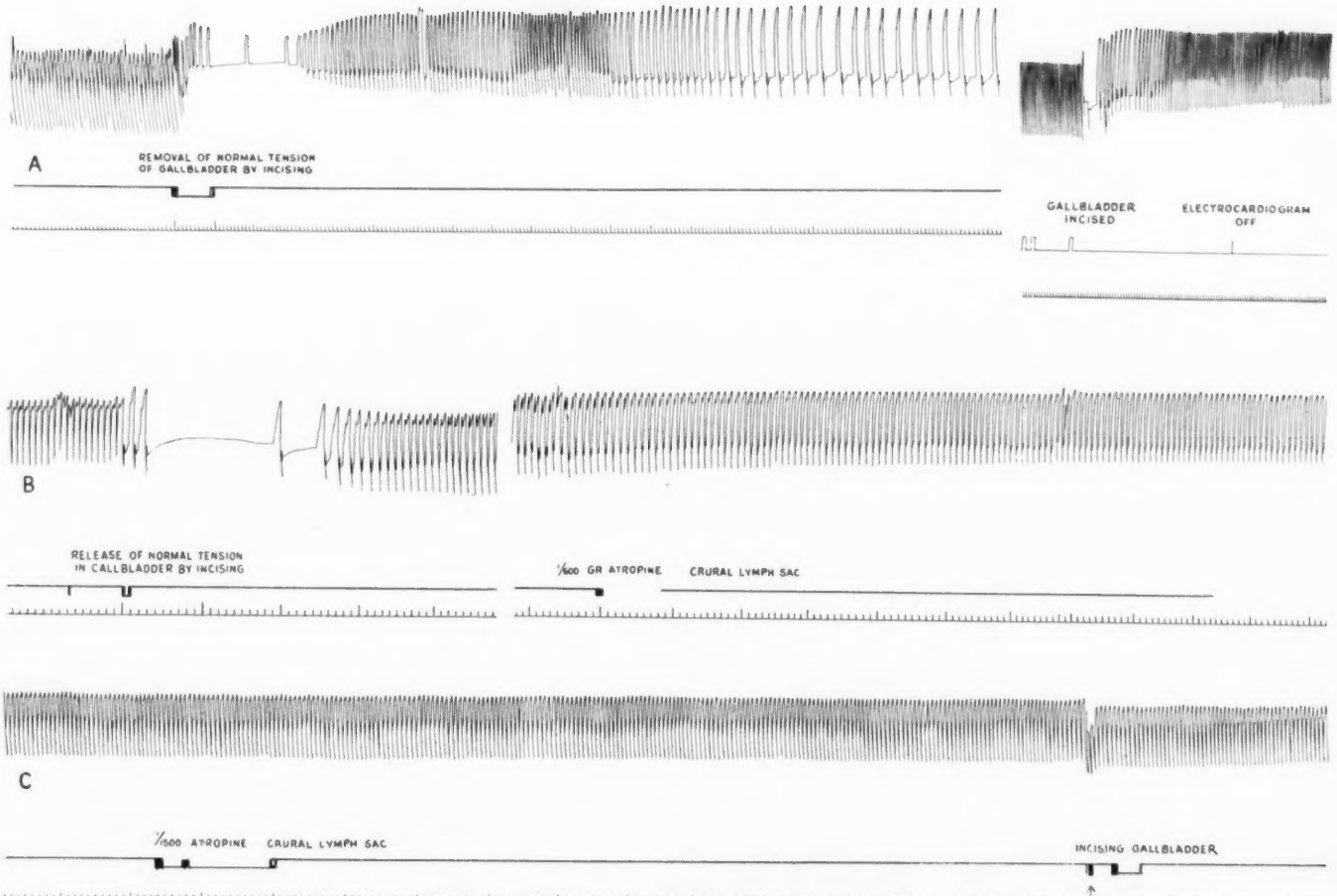

Fig. 6. Typical cardiac responses following incision into and release of bile from the gallbladder in the decerebrated frog. Following the incision

Fig. 6.—Typical cardiac responses following incision into and release of bile from the gallbladder in the decerebrated frog. Following the incision

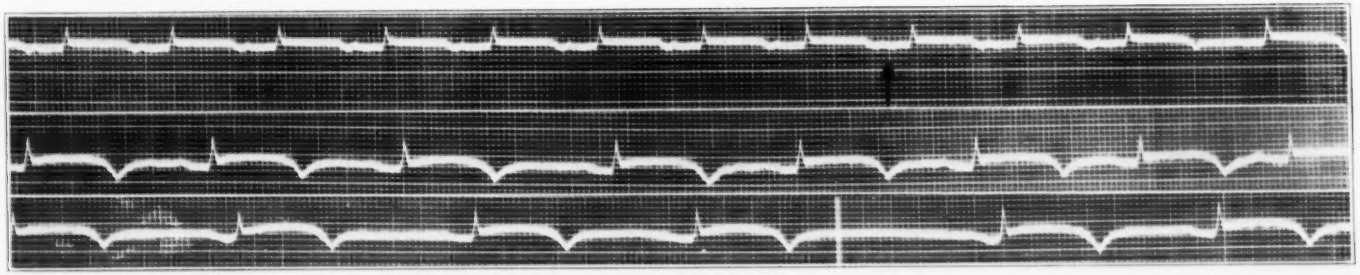

Fig. 7.—Continuous tracing showing sinus block and the inversion of the T-wave in the frog after the incision into and release of bile from the gallbladder. The electrodes were placed at the base and apex of the suspended heart.

Fig. 8.—Showing types of spontaneous arrhythmias that develop in frogs in which the common bile ducts were, for several days, previously

perhaps undue prominence given this symptom (Osler and McCrae,[4] Elliott,[5] Porter,[6] Allbutt,[7] Rolleston[8] and Umber[9]). A perusal of the literature, however, reveals important exceptions. Mackenzie[10] had never seen this symptom, although he had looked for it. Vaquez[11] stated that if a slowing of the heart occurs it is scarcely appreciable; in the experience of McVicar and Fitts,[12] bradycardia in jaundice "proved almost a myth." Windle[13] noted that in the vast majority of cases of obstructive jaundice the frequency of the heart was about or above the normal, but that catarrhal jaundice in young people was commonly associated with a slow pulse rate. The observations I have made on dogs are in harmony with those of Windle.

In the large literature dealing with the cardiovascular effects following the injection of bile constituents or whole bile, there is the strong evidence that the vagus plays some rôle in the slowing of the heart rate. To assume that a similar mechanism is operating in the intact, unanesthetized animal in which jaundice has been induced by ligation of the bile duct would be gratuitous. Granted, even, that they are similar, the basic experimental conditions are of a different nature, for in the former a state of jaundice, which implies a discoloration of the skin and mucous membranes, is not present. Moreover, such mechanical factors as may arise from acutely or chronically distended bile passages are necessarily obviated in the first type of experiment. It was customary in the past to attribute most forms of slowing of the heart rate to a vagus action, and in this respect jaundice does not form an exception. In view of the fact that the factor of age is definitely known to influence

4. Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1926.

5. Elliott, C. A., in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1925, vol. 7, p. 227.

6. Porter, L. A., in Ab, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 3, p. 645.

7. Allbutt, C. A.: A System of Medicine, London, The Macmillan Company, 1909, vol. 6.

8. Rolleston, H.: Diseases of the Liver, Gall Bladder and Bile Ducts, London, the Macmillan Company, 1912, p. 543.

9. Umber, F.: Erkrankungen der Leber und der Gallenwege, Handbuch der Inneren Medizin, Berlin, Julius Springer, 1918, p. 23.

10. Mackenzie, J.: A Study of the Pulse, London, The Macmillan Company, 1902; Diseases of the Heart, London, Oxford Medical Publications, 1921.

11. Vaquez, H.: Diseases of the Heart, trans. by G. F. Laidlow, Philadelphia, W. B. Saunders Company, 1924.

12. McVicar, C. S., and Fitts, W. T.: Clinical Aspects of Jaundice, J. A. M. A. **89**:2018 (Dec.) 1927.

13. Windle, J. D.: The Heart's Action in Jaundice, Brit. M. J. **1**:123 (Jan.) 1916.

the frequency of certain phenomena which have a vagal origin,[14] the observations that I have made on dogs would lend support to the vagal hypothesis of bradycardia in jaundice.

Apart from such indirect evidence, that furnished by the atropine test would indicate that in obstructive jaundice in puppies the original vagal tone is intensified. The absence of bradycardia in the adult dog could be explained on the basis of a less sensitive vegetative nervous system. The absence of any gross irregularity of the heart rate at the time of the slowing in puppies need not preclude a vagus action; Lewis [15] pointed out that the criterion of irregularity, although valuable, may not be absolute. It is conceivable also that the absence of respiratory variation of the heart rate may be due to increased vagal tone, since this form of arrhythmia may be regarded as evidence of an insignificant instability of tonic nerve action. An exaggeration of this phenomenon would more easily fit in with the accorded explanation. A selective action of one of the bile constituents on the sinus part of the genetic system is possible, but such is not afforded by the electrocardiogram. The PR interval was not prolonged in any case, and a change in the configuration of the P-wave was encountered in only one instance. While the inversion of the T-wave of the electrocardiogram obtained in frog experiments appeared to have a vagal origin, that noted in the puppies cannot so readily be conceded to have such a derivation. In the frogs, the electrodes were placed on the basal and apical portions of the heart, and Lewis, Meakins and White [16] called attention to the fact that one cannot be too circumspect in interpreting curves taken by direct leads. The appearance of the invert form so early after obstruction of the bile ducts in half the series studied electrocardiographically, its transitoriness and the reappearance in the electrocardiogram in the one animal at about the time of reestablishment of bile flow to the intestine suggest a functional origin, and not one due to structural change in the heart muscle.

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14. Gilbert (Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, Arch. Int. Med. **31**:423 [March] 1923), found that a marked slowing of the heart rate could most readily be produced in adults, especially in the sixth decade, and noted the infrequency of its occurrence in youthful subjects. Hering (Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe vom normal-physiologischen, pathologisch-physiologischen und Klinischen Standpunkt, Dresden and Leipzig, Theodore Steinkopff, 1927), however, pointed out that the vagus trunks in the neck are resistant to mechanical stimulation and that this reflex is due to a specific reflex. The focus for the sensory nerve distribution is what Hering calls the "carotid sinus."

15. Lewis, Thomas: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1925, p. 433.

16. Lewis, T.; Meakins, J., and White, P. D.; The Excitatory Process in the Dogs's Heart: I. The Auricles, Phil. T. Roy. Soc., London **205**:375, 1914.

The mechanical factor produced by acute and even more chronic distentions of the intrahepatic and extrahepatic ducts, particularly the sudden changes of intraductal pressure, have, up to the present, not received any consideration as a cause for the bradycardia in jaundice. I am of the opinion that this factor and possible injury of the liver produced in obstruction but particularly the former may play an exceedingly important rôle in furnishing a focus for the sensory nerve distribution of a part of the specific reflex, and acting through the vagus. Not only may such mechanism be contributive in initiating or maintaining a slowing of the heart rate in obstructive jaundice, but it may also be operating in the abnormal rhythms accompanying certain cases of cholelithiasis without frank jaundice. Straus and Hamburger [17] studied a group of the latter type of cases with the electrocardiogram.

In their studies of the visceral sensory nervous systems, Carlson and Luckhardt [18] did not readily obtain cardiac standstill in the frog by means of electrical or mechanical stimulation. They noted the complete and almost instantaneous inhibition following the mere touching of the urinary bladder and small intestine. Sherrington [19] pointed out that the main function of the receptor is to lower the threshold of excitability of the arc for one kind of stimulus and to heighten it for others. "It is necessary that the mechanical stimulation be adequate, and to be adequate it must be of a certain kind." The cardiac reflexes which I provoked in the frog by producing sudden changes in the intraductal pressure, following the release of bile after incision of the gallbladder, appear to be analogous to the vascular reflexes which Sherrington [20] strikingly provoked by mechanical distention transiently produced by the injection of a few cubic centimeters of saline solution into the bile ducts. This regularly evokes a marked rise of arterial pressure. Also, the early bradycardia that I noted in puppies, following the ligation of the common duct, could be explained on a similar basis, in light of the recent investigations of Bollman, Sheard and Mann,[21] who showed an almost immediate maximal intraductal pressure after ligation of the common duct.

17. Straus, D. C., and Hamburger, W. W.: The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholelithiasis, Cholecystitis, and Duodenal Ulcer, J. A. M. A. **82**:706 (March) 1924.

18. Carlson, A. J., and Luckhardt, A. B.: Studies of the Visceral Sensory Nervous System: V. Cardiac and Vasomotor Reflexes Induced by Visceral Stimulation in Amphibia and Reptilia, Am. J. Physiol. **55**:31 (Feb.) 1921.

19. Sherrington, C. S.: Integrative Action of the Central Nervous System, New York, Charles Scribner's Sons, 1906, p. 12.

20. Sherrington, C. S.: On the Spinal Animal, Marshall Hall Prize Address, Med.-Chir. Tr., 1899, vol. 82.

21. Bollman, J. L.; Sheard, C., and Mann, F. C.: An Experimental Study of Obstructive Jaundice with Particular Reference to the Initial Bilirubinemia, Am. J. Physiol. **80**:461 (April) 1927.

The same authors also demonstrated an early functional incapacity of the hepatic cells in the transference of bile pigment from the vascular capillaries into the bile capillaries. One must, therefore, also consider injury of the liver in jaundice as a possible cause for the slowing of the heart rate.

The early necrosis of hepatic cells after obstruction of the common duct was emphasized by Ogato.[22] Finsterer [23] called attention to the symptom bradycardia as being almost pathognomonic of injury to the liver. This problem, carried by him into the laboratory, yielded fruitful results. He found that bradycardia could most readily be produced by experimental lesions of the liver, in contrast to the acceleration invariably noted after contusions of the intestines, spleen and other viscera. He further noted that the bradycardia was not modified by atropine or section of the vagi. Recently, Ricciuti [24] reported on clinical bradycardia with lesions of the liver due to contusion; bradycardia was particularly marked in two cases of gunshot wounds of the liver. Straus [25] also noted bradycardia in clinical cases of contusion of the liver, but was unable to get anything like uniformly positive results in his experimental work on dogs (unpublished).

Pearcy and Howard [26] arrived at the conclusion that cardiac reflexes provoked by mechanical stimulation of abdominal viscera (and this included the mechanical distention of the gallbladder) must be of sympathetic origin. They noted that an extrasystolic arrhythmia was obtained equally well whether or not the vagi were intact; and that when the vagi were intact and the cord was cut "so as to eliminate the sympathetic system from participating in the reflex, the irregularities were never observed." My objections to such conclusions are as follows: In the first place, transection of the cord (the authors did not mention the site of transection, which is important, but I suppose it is at a high level) profoundly alters not only the cardiac but every other physiologic mechanism. The fact that reflex responses do not occur over the vagi after this procedure is not by any means indisputable proof that they may not occur in the intact animal. The experimental animals used

22. Ogato, T.: Beitrage zur experimentelle erzugten Lebercirrhose und zur Pathogenese des Ikterus mit spezieller Berücksichtigung der Gallenkapillaren bei der Unterbindung des Ductus cholesdochus unter der Ikterogenvergiftung, Beitr. z. path. Anat. u. z. allg. Pathol. **55**:236, 1913.

23. Finsterer, H.: Ueber Leberverletzungen, Deutsche Ztschr. f. Chir. **118**:1, 1913.

24. Ricciuti, G.: Bradicardia in ferite e lesione contusive del fegato, Policlinico (sez. chir.) **34**:229 (May) 1927.

25. Straus, D. C.: Personal communication to the author.

26. Pearcy, J. F., and Howard, H.: Studies on the Visceral Sensory Nervous System: XVIII. Reflexes from the Peritoneal Viscera to the Heart, Am. Heart. J. **2**:530 (June) 1927.

by Pearcy and Howard not only were treated with barbital, but were given sufficient doses of barium chloride, which of itself provoked extrasystoles before mechanical stimulation was begun. Lastly, they provoked not a tachycardia which would constitute a typical sympathetic response but an extrasystolic arrhythmia which is produced capriciously and only with the greatest difficulty by sympathetic stimulation.

There has been almost unanimity of opinion that some central depression occurs in obstructive jaundice. I [27] attributed the amelioration of the symptoms of tetany and the delay in their appearance in the parathyroidectomized animal which had been jaundiced for some time previously to central depression. Working more recently with picrotoxin, a violent medullary stimulant, I was not able to note any appreciable differences in the time of appearance or in the pattern of the preconvulsive and convulsive seizures in the jaundized and nonjaundiced dog, although the drug was administered to the former when there appeared to be depression. The question of depression of cardiovascular function has also been raised, and it has been customary to attribute to it not only the slowing of the heart rate, but also the slower respirations.

When bradycardia occurs in the puppy shortly after the induction of jaundice, there is but little change in the activity and behavior of the animal. Even when the animal becomes apathetic and inactive and shows depression, at least in spirits, bradycardia does not exist, and there is an acceleration of the heart. At this time, there appear to be definite evidences of cardiac failure which are manifested in the tachycardia, the presence of murmurs and the dyspnea which may occur independently of ascites. From such observations one should be unwilling to subscribe to the prevalent view that bradycardia occurring in jaundice is due to central depression.

Mention should also be made of the disturbances of the calcium metabolism that arise in obstructive jaundice, and of possible cardiac effects resulting from changes in the ionic equilibria of the blood and tissues. I have called attention to the marked decrease in the blood serum calcium in the jaundiced puppy. King, Bigelow and Pearce [28] suggested that so far as their quantitative studies of the calcium balance in obstructive jaundice show a marked loss of this substance from the heart muscle, the slowing of the heart rate in jaundice may be due to the removal of the stimulating force from this organ. The special

27. Buchbinder, W. C., and Kern, R.: Experimental Obstructive Jaundice: II. A Modification of the Tetany Mechanism in Jaundice, Arch. Int. Med. **41**:754 (May) 1928.

28. King, J. H.; Bigelow, J. E., and Pearce, L.: Experimental Obstructive Jaundice, J. Exper. Med. **14**:159, 1911.

affinity which the heart discloses for calcium [29] in hypercalcemic states, following the use of Collip's extract, makes the question of a possible loss of calcium from the heart in jaundiced states a mooted one. It is to be noted that the initial marked bradycardia is not associated with any quantitative change in the blood serum calcium. The first evidence of the latter's decrease is concomitant with a relative tachycardia. If it is correct that at this time there is a loss of calcium from the heart muscle, I believe that any possible effects of such would be overshadowed by a direct poisoning of the heart muscle. Since the adult jaundiced dog does not manifest any significant change in the heart rate, and discloses a normally constant blood serum calcium, the question remains of great interest.

Finally, a brief consideration of the possible mechanisms involved in the production of the characteristic trend of the heart rate in jaundiced puppies must not be omitted. I have merely attempted to offer a plausible and convenient explanation to fit the facts. It is believed that the slowing of the heart rate in jaundiced puppies is a specific reflex through the vagus, and that the mechanically distended intrahepatic and extrahepatic ducts serve as a focus for visceral stimulation. The reflex slowing is unimpeded during the first five or ten days by any of the metabolites arising as a result of the obstruction. The query raised by Carlson [30] whether the persistence of an abnormal reflex for so long a time would be unusual constitutes, to my mind, the most valid objection to such an hypothesis. The second period, that of relative tachycardia, represents the first poisoning effects of bile (presumably the bile salts) on the heart. The acceleration, however, is more than counterbalanced by the heart slowing mechanism suggested previously, and the heart rate during a considerable period of the jaundice remains slower than in the normal animal. The third period of absolute tachycardia represents a direct marked poisoning of the heart muscle by metabolites, and this is associated with a depression and toxemia.

SUMMARY

The trend of the heart rate of puppies subjected to ligation and division of the common bile duct is such as may be conveniently divided into three periods: (1) one of an initial marked bradycardia, (2) one of relative tachycardia and (3) one of absolute tachycardia.

An inconspicuous, or absent respiratory variation of the heart rate is noted in the jaundiced puppy, especially in the middle or later periods of obstruction.

29. Collip, J. B.: Harvey Lectures, Baltimore, Williams & Wilkins Company, 1925, p. 142.

30. Carlson, A. J.: Personal communication to the author.

Inversion of the T-wave is the most common abnormality in the electrocardiogram of the jaundiced puppy. It is thought to have a functional origin rather than one resulting from organic changes in the heart muscle.

Bradycardia does not occur in the adult dog subjected to ligation and division of the common bile duct. A slight degree of acceleration is the rule. The absence of bradycardia under these circumstances is explained on the basis of a less sensitive vegetative nervous system.

Bradycardia in the puppy is unassociated with apparent marked central depression, which is characteristically present in the late periods of obstruction when acceleration is the rule.

In the decerebrated frog, there is a specific reflex from the gallbladder to the heart. In order to evoke it, the stimulation must be "adequate." Acute changes in pressure in the bile tracts is thought to constitute an "adequate stimulus." Spontaneous arrhythmias, with sudden halving of the rate, frequently occur in the suspended hearts of frogs, which for several days have had a ligation and divsion of their common bile ducts.

The temptation arises to explain the initial marked bradycardia that occurs in jaundiced puppies on the basis of a specific reflex, the mechanically distended intrahepatic and extrahepatic ducts serving as a focus for visceral sensory stimulation. The reflex is thought to be through the vagus.

SECRETIN NOT A HEMATOPOIETIC STIMULANT *

J. T. KING, M.D.
MINNEAPOLIS

The present intense interest in substances thought to have a stimulating influence on blood-forming tissues again emphasizes the need for a clearly defined set of criteria by which to judge regeneration.

The picture of a true regeneration is best seen following hemorrhage in the healthy animal. Table 1 gives the data on two experiments in

TABLE 1.—*Results of Two Experiments in Which the Blood Count in the Rabbit Was Reduced by Hemorrhage*

Experiment Number	Date	Red Blood Cells	White Blood Cells	Reticulocytes	Experimental Procedure
50	2/ 9	4,190,000	6,850	11	Bled 34 cc. from the vein of the ear
	10	2,590,000	6,400	22	
	11	2,490,000	5,400	74	
	12	3,130,000	5,050	73	
	13	2,740,000	5,750	144	
	14	2,980,000	8,150	135	
	15	2,750,000	4,700	166	
	16	3,330,000	10,250	154	
	17	3,510,000	6,000	126	
	18	3,350,000	5,500	51	
	19	3,520,000	7,550	56	
	20	3,310,000	3,850	62	
	21	4,200,000	6,750	64	
	23	4,110,000	6,800	26	
	4/ 9	6,450,000	14,700	10	
51	2/ 9	4,520,000	10,450	25	Bled 18 cc. from the vein of the ear
	10	3,570,000	9,550	26	
	11	3,920,000	11,350	74	
	12	3,570,000	8,800	101	
	13	3,580,000	16,400	84	
	14	3,379,000	10,100	84	
	15	4,100,000	9,650	75	
	16	4,330,000	6,600	72	
	17	4,180,000	9,100	52	
	18	4,040,000	7,500	50	
	19	3,960,000	10,100	68	
	20	4,270,000	6,500	58	
	21	4,320,000	8,600	99	
	23	4,810,000	.....	51	
	4/ 9	6,370,000	13,400	12	

which the blood count in the rabbit was reduced by hemorrhage. The experiments extend over the recovery period; leukocyte and reticulocyte counts are given. The two points to be especially noted are that rise in red count due to regeneration is slow, and that histologic evidence of regeneration, as indicated by the rise in reticulocytes, is unmistakable. Stained smears show an increase in the number of polychromatophilic cells, and when regeneration is active nucleated reds may appear.

As a contrast to this picture of true regeneration, with the slowly rising count accompanied by an increase of reticulocytes and polychro-

* Submitted for publication, July 31, 1928.

* From the Department of Physiology, University of Minnesota.

matophilic cells, one may cite the rapid rise in count known to follow the injection of such substances as histamine or tissue extracts in general. In this case, the red count rises rapidly, reaches its maximum in most cases between one and two hours and then returns gradually to the original level. The time required for the whole reaction is relatively short, being on the average from three to four hours. If such substances are given intravenously, much less time is required. Table 2 gives data on an experiment in which 50 cc. of secretin, an acid extract of intestinal mucosa, was injected intravenously into a dog under ether anesthesia. It is seen that the count rose rapidly to a maximum and then returned promptly to normal. This rapid rise and fall in red count, unaccompanied by any histologic signs of regeneration such as increase in reticulocytes or polychromatophilic cells, is char-

TABLE 2.—*Results of an Injection of 50 cc. of Secretin Into a Dog Under Ether Anesthesia*

Time, P. M.	Red Blood Cells	Remarks
3 : 20	7,030,000	Ether anesthesia started at 3 p. m. Initial high count probably due to struggle during induction of anesthesia.
3 : 30	6,620,000	
4 : 08	6,540,000	
4 : 11	6,550,000	
4 : 27 to 4 : 35	.....	50 cc. secretin
4 : 40	6,480,000	
4 : 43	7,440,000	
4 : 50	7,680,000	
5 : 03	7,300,000	
5 : 17	7,030,000	
5 : 28	6,550,000	
5 : 38	6,030,000	
5 : 40	.....	Killed by cholorform

acteristic of the reaction to tissue extracts. The explanation of the increase in count is not that new cells are produced, but that the blood is temporarily concentrated owing to the escape of plasma from the vascular system. The evidence on this problem will be presented.

In this study the reticulocyte count, as well as the usual smears stained with Wright's stain, was used in judging the activity of the blood-forming tissues. The reticulocyte is seen as a red cell which contains a characteristic bluish substance present in variable form and amount. Only a granule or two may be seen in some cells, while others may contain a large amount of the substance in the form of a net or filaments. This bluish substance, which is precipitated by the dye, is seen in a diffuse form in the ordinary blood smear stained with Wright's stain. The whole cell containing it is blue. This is the well known polychromatophilic cell, which has been recognized for a long time as being present in increased numbers whenever the blood-forming tissue is stimulated to increased cell production.

REVIEW OF LITERATURE

The term "reticulocyte" was suggested by Krumbhaar [1] to designate what had been referred to as the reticulated erythrocyte. At the same time, he suggested the term reticulosis to designate an increased number of reticulocytes in the peripheral blood. His paper contains data on normal counts and variations in some experimental conditions. He pointed out that the figures usually given for man are rather high, and set the normal between 0.1 and 1 per cent. It was also pointed out that the reticulocyte count in the infant soon falls to a figure close to that of the adult. Some data on laboratory animals are given.

In 1921, Key [2] published a work on the significance of the reticulum found in these cells and its relation to basophilic stippling and polychromatophilia. The work is comprehensive and should be read by any one interested in this subject.

The reticulocyte lends itself more readily to quantitative estimation than does the polychromatophilic cell. This is due to the fact that variations in staining technic are not so apt to influence the reticulocyte count. Then, too, the personal factor is not so important in the counting of reticulocytes, as the observer is determining the presence or absence of definite cell inclusions, while in the case of the polychromatophilic cell, one has to decide on the basis of slight differences in color caused by a diffusely distributed substance. It is worthy of note that the reticulocyte count is being accepted as the criterion of marrow response by the many workers who are using liver and liver extracts in the treatment of pernicious anemia.

Technic.—Reticulocyte counts were made on fresh preparations. The technic used is that given by Robertson.[3] The blood is drawn into a pipet containing a dilute solution of brilliant cresyl blue in saline solution. After the pipet is shaken and allowed to stand for a few minutes, a drop of the blood is placed on a slide, quickly covered with a thin cover and sealed with petrolatum. The preparation is then examined with the oil immersion lens, and the reticulocyte count is expressed as the number present in 1,000 cells or in percentage.

In a series of papers,[4] Downs and Eddy recorded the observations which led them to conclude that secretin is a stimulant of blood-forming

1. Krumbhaar, E. B.: Reticulosis—Increased Percentage of Reticulated Erythrocytes in the Peripheral Blood, J. Lab. & Clin. Med. **8**:11, 1922.

2. Key, J. A.: Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. **28**:511 (Nov.) 1921.

3. Robertson, O. H.: The Effects of Experimental Anemia on Blood Production, J. Exper. Med. **26**:221, 1917.

4. Downs, A. W., and Eddy, N. B.: The Influence of Secretin on the Number of Erythroyctes in the Circulating Blood, Am. J. Physiol. **43**:415, 1917; Secretin: II. Its Influence on the Number of White Corpuscles in the Circulating Blood, ibid. **45**:294, 1918; Secretin: III. Its Mode of Action in Producing an Increase in the Number of Corpuscles in the Circulating Blood, ibid. **46**:209, 1918.

tissue. They observed a rapid increase in the number of red and white corpuscles in the peripheral blood of the rabbit after subcutaneous injections of 10 mg. of secretin per kilogram of body weight. The increase in red blood cells was about 20 per cent, and the height of the reaction occurred about an hour after the injection, the count then returning to normal. The whole reaction was complete in approximately three hours. They believed the rise in count to be due to the production of new blood cells.

Fujimoto [5] later checked these results. After the injection of secretin, he recorded a minimum rise of 5 per cent and a maximum rise of 64 per cent, the average being 25.75 per cent. The increase in white

TABLE 3.—*Author's Data on the Stimulating Effect of Secretin on the Blood*

Experiment Number	Initial Count	Maximum Count	Gain
21	6,280,000	6,900,000	620,000
22	5,420,000	6,920,000	1,500,000
23	5,610,000	7,150,444	1,540,000
24	6,400,000	6,920,000	440,000
25	5,510,000	6,160,000	650,000
26	6,020,000	6,510,000	490,000
27	4,390,000	6,430,000	2,040,000
28	5,940,000	6,170,000	1,230,000
29	5,270,000	5,440,000	170,000
30	4,930,000	5,060,000	130,000
31	3,370,000	3,630,000	260,000
32	4,030,000	4,340,000	310,000
33	4,660,000	5,430,000	770,000
34	5,030,000	5,690,000	660,000
35	7,130,000	7,390,000	260,000
36	4,510,000	4,640,000	130,000
37	4,500,000	5,320,000	740,000
38	4,650,000	4,920,000	270,000
39	4,500,000	5,140,000	640,000
40	4,980,000	5,230,000	250,000
41	4,800,000	4,970,000	170,000
42	4,850,000	4,910,000	6,000
Average	5,179,090	5,776,360	597,270
Average gain	11.1%		

cells varied from 3 to 96 per cent, the average being 34.75 per cent. My data on similar experiments are given in table 3. The experiments were included whether there was marked or little response.

Downs and Eddy's observations on the increase in number of corpuscles in the peripheral blood of the rabbit following the injection of secretin are corroborated. Their conclusion, however, that the rise is due to the production of new blood cells is surprising in view of many well known facts concerning regeneration.

There is no clinical or experimental evidence which would lead one to believe that an increase of a million or more cells per cubic millimeter of peripheral blood, taking place in about an hour and then returning

5. Fujimoto, B.: The Influence of Secretin on the Number of Red and White Corpuscles and the Ferments and Sugar Content of the Blood, Am. J. Physiol. **47**:342, 1918.

promptly to normal, could possibly be due to regeneration of new cells by the blood-forming tissues. All available evidence indicates that any rise in blood counts due to regeneration of new cells is slow, and, moreover, is not followed promptly by a return to the former level.

Lamson [6] warned against regarding rapid changes in blood counts as due to the production of new cells. He said, "The fact that an increase of one million or more in the number of erythrocytes per cubic millimeter of blood takes place in from five to ten minutes, disappears in about an hour and may be repeated many times a day, is against the production of new cells, a decreased destruction or division of erythrocytes."

Scott [7] emphasized the changes in concentration of the blood due to fluid exchange between the blood and tissue spaces.

Downs and Eddy's data show that by using intravenous injections they obtained increases as high as 40 per cent in as short a time as thirty-one minutes.

Hammett and Nowrey,[8] working on the erythropoietic activity of germanium dioxide, called attention to the fact that the rise in red count which they used as a criterion of regeneration is not a transient reaction, but one which persists from eleven days to five weeks. This rise, moreover, is accompanied by other acceptable signs of regeneration, namely, "many polychromatic staining cells or young red cells."

Minot and Sampson [9] published a work which contains valuable criticism of unwarranted deductions drawn from increased red counts by workers experimenting with hematopoietic stimulants. They pointed out that "merely an increase in the number of red cells in the circulation is ordinarily no indication of increased blood formation." Again, "Many of the red cell rises reported were moderate and transient and do not appear to have been controlled by a sufficient number of observations prior to administration."

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6. Lamson, P. D.: The Part Played by the Liver in the Blood Volume and Red Corpuscles Concentration in Acute Physiological Conditions, J. Pharmacol. & Exper. Therap. **16**:125, 1920.

7. Scott, F. H.: Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces: I. Blood Pressure, Am. J. Physiol. **44**:298, 1917. Scott, F. H.; Herrmann, E. T., and Snell, A. M.: Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces: II. Muscular Activity, Am. J. Physiol. **44**:313, 1917.

8. Hammett, F. S., and Nowrey, J. E.: The Erythropoietic Action of Germanium Dioxide: II. The Source of the Erythrocythemia Produced by Germanium Dioxide in the Albino Rat, J. Exper. Med. **35**:507, 1922.

9. Minot, G. R., and Sampson, J. J.: Germanium Dioxide as a Remedy for Anemia, Boston M. & S. J. **189**:629, 1923.

Braun,[10] working on blood destruction, made the following statement: "But, as is well known, stimulation of marrow, even after considerable blood losses by hemorrhage, is not effective at once. Only after several days does the replacement of the lost corpuscles go on actively."

The work of Whipple, Robscheit and Hooper,[11] who studied the effect of various procedures on regeneration after hemorrhage, emphasizes the fact again that even under the best conditions the delivery of new cells to the circulation is a slow, gradual process. "Anemia is produced by bleeding one fourth of the measured blood volume on each of two successive days. This anemia will be completely repaired within three to four weeks if the dog is given a liberal diet of meat or beef heart."

Table 4 is taken from Bunting's work.[12] This shows the length of time required to regenerate about 1,000,000 new cells.

TABLE 4.—*Results of Bunting's Experimental Work*

Date	Red Blood Cells	White Blood Cells	Experimental Procedure
4/27	5,416,000	14,750	Bled 30 cc. from the vein of the ear
4/28	4,736,000	12,250	
29	4,904,000	17,250	
5/ 1	4,760,000	19,600	
5	5,368,000	9,125	
7	5,752,000	13,000	

Table 1 gives some data I obtained by the production in rabbits of various degrees of hemorrhage.

It is obvious that such rapid and transient rises in count as were observed by Downs and Eddy must be explained on some basis other than the production of new blood cells. One has only to consider the well known facts concerning the so-called solutions of secretin used to be convinced that the rises they observed were due to a concentration of the blood, and, furthermore, that such concentration was due not to the secretin contained in the solution, but to some of the many other substances inevitably present in such a tissue extract.

The tissue extract containing secretin is prepared as follows:

The upper part of the small intestine of the dog is washed; the mucous membrane is removed and ground up with sand. Fifty cc. of 0.5 per cent hydrochloric acid is then added; after standing for two hours, the mixture is boiled actively.

10. Braun, G. O.: Blood Destruction During Exercise: II. Demonstration of the Blood Destruction in Animals Exercised After Prolonged Confinement, J. Exper. Med. **37**:113, 1923.

11. Whipple, G. H.; Robscheit, F. S., and Hooper, C. W.: Blood Regeneration in Simple Anemia: IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets, Am. J. Physiol. **53**:236, 1920.

12. Bunting, C. H.: Experimental Anemias in the Rabbit, J. Exper. Med. **8**:625, 1906.

After it has been neutralized with sodium hydroxide and reacidified with acetic acid, it is strained through muslin and filtered. The resulting fluid is usually described as yellowish or greenish yellow and slightly opalescent.

Carlson, Lebensohn and Pearlman [13] stated: "In a maceration of duodenojejunal mucosa such as we have in secretin, the known substances are proteoses and peptones, acid amins, bile salts, beta-imidazolethylamin (histamine), choline, gelatin and inorganic salts."

Early in the experimental work with rabbits it was noted that there was a reaction which varied considerably with different animals and different doses. At times the animals appeared dyspneic; at times there was uneasiness which passed off and might even be followed by apathy, and occasionally salivation was noted.

Dogs were used in order to check the strength of the secretin. A cannula was placed in the pancreatic duct, and the drops of pancreatic juice were recorded by an electric drop recorder. Tracings of the blood pressure were taken simultaneously. The secretin solutions were given intravenously. Doses of sufficient size to stimulate the pancreas to any extent had a marked lowering effect on the blood pressure. Immediately following injection, there was unusually violent peristalsis and frequently breathing was rapid for a time. If more than 10 cc. of the solution was injected quickly, especially if it was the first injection, the animals frequently died at once. Death was apparently due to cardiac failure. When the thorax was opened and the heart was examined, the ventricles were found to be in a state of violent fibrillation, which at times also involved the auricles.

Even these simple observations serve to show that one is dealing with some potent substance or substances. One quickly surmises that the hormone secretin is not responsible for these unusual physiologic effects. In fact, it is a simple matter to prove this point. If 25 cc. of 5 per cent hydrochloric acid is injected into the duodenum, a comparable flow of pancreatic juice is obtained without the appearance of any of the phenomena mentioned.

It is probable that much more of the hormone secretin is liberated in the ordinary process of digestion than was administered by Downs and Eddy. Yet there is no reason to believe that the blood-forming tissues are stimulated to such an extent that the red count rises 20 per cent owing to the secretin liberated during digestion. Furthermore, Matsuo [14] stated that "secretin administered subcutaneously, even in large quantities, is practically without effect." Carlson, Lebensohn and Pearlman [13] stated that the hormone must be given intravenously to be

13. Carlson, A. J.; Lebensohn, J. E., and Pearlman, S. J.: Has Secretin a Therapeutic Value? J. A. M. A. **66**:178 (Jan. 15) 1916.

14. Matsuo, I.: On the Secretion of Pancreatic Juice, J. Physiol. **45**:447, 1913.

effective. One can only conclude that the hormone, secretin, contained in the tissue extract used subcutaneously, did not play any part in the changes noted by Downs and Eddy.

It is necessary at this point to consider the facts known concerning the physiologic effects of the tissue extract containing secretin in order to explain the nature of the increased counts observed by Downs and Eddy. In the foregoing it was stated that such an extract contains proteoses, peptones, acid amines, bile salts, histamine, choline, gelatin and inorganic salts.

Histamine was studied by Dale and Laidlaw [15] in 1910. They made the following statement:

> Mention may be made at this point of the fact that preparations such as Witte's peptone and various organ extracts, resemble beta-iminazolylethylamine (histamine) in their action on the uterus as well as in other respects. Figure 18 shows the effect on the isolated uterus of a virgin guinea-pig of adding to the bath 0.1 Gm. of Witte's peptone dissolved in warm Ringer's solution. The effect is indistinguishable from that of 0.1 mg. of iminazolylethylamine. Five-tenths cc. of an extract of intestinal mucosa (containing also secretin) had a precisely similar effect.

Barger and Dale [16] reported the isolation of histamine from intestinal mucosa in an article entitled, "Beta-iminazolylethylamine, A Depressor Constituent of Intestinal Mucosa." They also noted that histamine increased the flow of lymph from the thoracic duct.

It has been noted by others that tissue extracts (containing also secretin) cause increased flow of lymph from the thoracic duct. Mendel and Thacher [17] found that "the injection thus gave rise to an increased flow of lymph somewhat richer in solids—a feature characteristic of the action of certain lymphagogues."

Bainbridge [18] also reported the increase in flow of lymph but was inclined to believe that it was due to the activity of the pancreas and, therefore, to secretin itself rather than to contaminating substances. He stated, however, that ileum extract (which presumably does not contain secretin) also causes the increased flow if the portal lymphatics are not ligated. In a later work [19] on the flow of lymph observed in dogs post mortem, the same author stated, "The postmortem lymph

15. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of β-Iminazolylethylamine, J. Physiol. **41**:318, 1910.

16. Barger, G., and Dale, H. H.: β-Iminazolylethylamine, a Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1911.

17. Mendel, L. B., and Thacher, H. C.: On Secretin and Lymph Flow, Am. J. Physiol. **9**:16, 1903.

18. Bainbridge, F. A.: The Lymph Flow from the Pancreas, Brit. M. J. **2**: 1742, 1904.

19. Bainbridge, F. A.: The Postmortem Lymph Flow, J. Physiol. **34**:275, 1906.

flow after the injection of peptone is due either to filtration through abnormally permeable capillaries or to increased metabolism in the liver, the former view being the more probable."

Underhill and Ringer [20] stated:

> It has long been known that the intravenous injection of "Witte Pepton" induces low blood pressure and a shock-like condition, which are accompanied by changes in the blood coagulation and an increased flow of lymph. . . . It may be assumed that the direct cause of the blood concentration is the exit of fluid from the capillaries into the surrounding tissues which would account probably for the accelerated lymph flow. . . . Dale and his collaborators have shown that with histamine there is a capillary damage due to the drug and the fall of pressure due to histamine is without effect per se. . . . It is probable that peptone in itself changes the permeability of the capillaries in a manner analogous to that of histamine.

The data of these authors show that with both histamine and peptone there is considerable concentration of the blood which varies in degree and time relations with the dose used and the rapidity of injection. With peptone alone, the hemoglobin content may rise nearly 40 per cent. The usual rise was between 20 and 30 per cent. The injection of 0.5 Gm. per kilogram of deuteroproteoses caused a similar concentration. Histamine, likewise, causes a concentration which reaches a maximum more quickly and returns to normal more quickly.

The same authors, in another article,[21] reported their observations on "Vaughn's crude soluble poison." They found that it concentrated the blood in a manner somewhat similar to histamine. They noted the striking resemblances between the physiologic actions produced by this substance or substances and those produced by histamine.

Table 2 shows the results of the injection of an ordinary secretin solution intravenously into a dog.

The foregoing statements will serve to call attention to the marked similarity in the physiologic reaction caused by such substances as histamine, peptone and proteoses and such a tissue extract as the so-called secretin, which is a mixture of all these and more. The common response to such substances is a concentration of the blood. Usually, an increased flow of lymph is also noted. The concensus of opinion indicates that a change in capillary permeability is the essential factor in this reaction.

One may summarize at this point by stating that the rapid and transient rise in blood count which Downs and Eddy observed to

20. Underhill, F. P., and Ringer, M.: Studies on the Physiological Action of Some Protein Derivatives: V. The Relation of Blood Concentration to Peptone Shock, J. Pharmocol. & Exper. Therap. **19**:163, 1922.

21. Underhill, F. P., and Ringer, M.: Studies on the Physiological Action of Some Protein Derivatives: VI. The Influence on Blood Concentration of Vaughn's Crude Soluble Poison, J. Pharmacol. & Exper. Therap. **19**:179, 1922.

follow injection (subcutaneous) of secretin is not characteristic of regeneration but is of the type known to occur after the administration of such substances as histamine, peptones and proteoses. The solutions used by Downs and Eddy are known to contain these and other substances. As the hormone secretin is not effective when given subcutaneously, one must assume that the concentration observed was caused by one or more of the other substances.

Thus far, attention has been confined to the first two papers by Downs and Eddy.[22] Evidence has been advanced in support of two points: (1) that rapid and transient rises in blood count are not

TABLE 5.—*Results of Downs and Eddy's Experiments on Rabbits Which Received Secretin and Control Rabbits*

Number	Blood Cells	Initial Count	First Week Average	Second Week Average	Third Week Average	Fourth Week Average	Fifth Week Average	Sixth Week Average	Seventh Week Average	Eighth Week Average
					"Secretin" Rabbits					
1	White.	9,300	17,183	22,166	22,266	25,833	29,300	16,250	17,400	13,100
	Red...	6,608,000	5,929,000	4,703,000	6,156,000	5,178,000	6,858,000	6,300,000	6,944,000	7,562,000
2	White.	10,400	12,866	12,916	26,133	20,333	13,000	14,200	16,950	14,000
	Red...	4,432,000	4,941,000	5,208,000	6,150,000	5,042,000	6,715,000	6,336,000	7,196,000	7,332,000
*	White.	9,850	15,024	17,541	24,199	22,933	21,150	15,125	17,150	13,550
	Red...	5,520,000	5,435,000	4,955,500	6,150,000	5,110,000	6,786,500	6,318,000	7,070,000	7,447,000
†	White.	100.00	152.52	178.68	246.69	232.82	214.63	153.55	174.03	137.53
	Red...	100.00	98.46	89.77	111.41	92.57	122.94	114.45	128.07	134.90
					Control Rabbits					
3	White.	7,100	7,833	7,166	11,800	7,833	7,600	6,800	9,000	8,533
	Red...	6,272,000	5,536,000	5,784,000	6,121,000	5,386,000	6,333,000	6,574,000	6,616,000	7,250,000
4	White.	9,800	9,166	6,916	9,100	9,600	10,100	11,250	12,600	10,433
	Red....	6,176,000	6,081,000	6,194,000	6,253,000	6,377,000	7,530,000	6,856,000	6,481,000	7,244,000
*	White.	8,450	8,499	7,041	10,450	8,716	8,850	9,025	10,800	9,483
	Red....	6,224,000	5,808,500	5,989,000	6,187,000	5,886,500	6,933,000	6,715,000	6,548,500	7,247,000
†	White.	100.00	100.57	83.31	123.66	103.14	104.73	106.80	127.69	112.22
	Red....	100.00	93.35	96.25	99.44	94.60	111.39	107.89	105.21	116.43

* Averages.
† Percentge relations.

characteristic of changes due to production of new cells; (2) that the solutions used contained substances (other than the hormone secretin) which are known to cause temporary concentrations of the blood resulting in rapid and transient rises in count such as Downs and Eddy observed.

Their third paper[23] presents data obtained from an experiment planned to explain the mode of action of secretin.

Four rabbits were used. Two were given forty doses of secretin, and the controls were given saline solution. The experiment extended over eight weeks, the observations being made several times each week. The data are given in table 5.

22. Downs and Eddy (footnote 4, first and second references).

23. Downs and Eddy (footnote 4, third reference).

COMPARISON OF RESULTS

I repeated the experiment with twice as many animals. The following differences in technic should be mentioned: The animals in my "secretin" group received thirty-seven doses of secretin, while those of Downs and Eddy received forty doses. Fresh solutions were used.

TABLE 6.—*Results of Author's Experiments on Rabbits Which Received Secretin and Control Rabbits*

"Secretin" Rabbits

Number	Blood Cells	Initial Count	First Week Average	Second Week Average	Third Week Average	Fourth Week Average	Fifth Week Average	Sixth Week Average	Seventh Week Average	Eighth Week Average
29	Reticulocytes	.....	16	25	30	41	60	60	37	37
	White.	.....	.....	10,400	12,400	10,900	10,250	16,300	13,350	10,450
	Red....	6,143,000	6,430,000	6,850,000	5,580,000	5,070,000	5,430,000	5,810,000	6,160,000	6,910,000
33	Reticulocytes	.....	11	15	44	43	31	40	47	26
	White.	.....	.....	12,200	18,500	14,700	13,350	13,450	22,550	16,500
	Red....	5,675,000	5,710,000	6,070,000	4,840,000	6,160,000	5,840,000	5,790,000	7,340,000	7,460,000
34	Reticulocytes	.....	6	11	34	45	62	45	39	47
	White.	.....	.....	11,200	12,700	17,650	12,200	14,500	15,900	13,050
	Red....	5,203,000	5,100,000	5,330,000	4,910,000	5,560,000	4,770,000	5,110,000	5,690,000	5,550,000
44	Reticulocytes	.....	12	29	43	37	48	60	58	28
	White.	.....	.....	11,650	11,700	11,950	13,080	13,100	13,150	13,150
	Red....	5,220,000	5,350,000	4,090,000	4,879,000	4,900,000	5,270,000	4,550,000	5,650,000	5,400,000
*	Reticulocytes	.....	11.25	20.00	37.75	41.50	50.25	51.25	45.25	34.50
	White.	.....	.....	11,375	13,825	13,800	12,200	14,337	16,237	13,287
	Red....	5,560,500	5,647,000	5,595,000	5,050,000	5,422,500	5,327,000	5,315,000	6,210,000	6,330,000

Final count 113.8% of the initial count.

Control Rabbits

Number	Blood Cells	Initial Count	First Week Average	Second Week Average	Third Week Average	Fourth Week Average	Fifth Week Average	Sixth Week Average	Seventh Week Average	Eighth Week Average
23	Reticulocytes	.....	.....	18	42	17	23	51	63	28
	White.	.....	17,000	12,200	13,600	21,500	10,900	11,550	9,000	9,150
	Red....	5,400,000	5,700,000	4,360,000	5,100,000	6,530,000	5,520,000	4,960,000	6,130,000	6,240,000
28	Reticulocytes	.....	34	18	50	25	25	38	62	38
	White.	.....	14,250	16,400	17,700	9,400	20,250	7,650	11,500	9,050
	Red....	6,236,000	6,260,000	6,230,000	5,400,000	5,550,000	5,900,000	5,780,000	7,060,000	6,740,000
38	Reticulocytes	.....	12	4	27	17	22	26	46	18
	White.	.....	28,800	25,800	29,050	27,050	22,050	35,300	22,000	16,700
	Red....	6,693,000	7,470,000	6,390,000	6,500,000	6,550,000	6,970,000	7,430,000	7,990,000	8,080,000
40	Reticulocytes	.....	21	7	34	25	31	54	48	49
	White.	.....	10,900	12,050	12,050	11,000	18,450	8,900	14,900	14,850
	Red....	5,433,000	5,660,000	5,030,000	4,230,000	4,110,000	4,480,000	4,550,000	5,260,000	5,670,000
*	Reticulocytes	.....	22.30	11.75	33.25	21.00	25.25	42.25	54.75	33.25
	White.	.....	17,737	16,608	18,100	17,237	18,412	15,800	14,375	12,437
	Red....	5,940,500	6,272,500	5,502,500	5,320,000	5,685,000	5,717,500	5,680,000	6,610,000	6,682,500

Final count 112.5% of the initial count.

* Averages.

The controls were injected with saline solution thirty-four times. The data are presented in table 6.

Downs and Eddy's "secretin" group finished the experiment with a red count which was 134.9 per cent of the initial count; the controls finished at 116.43 per cent. My "secretin" group finished at 113.8 per cent, while the control count was 112.5 per cent. Downs and Eddy felt

justified in assuming that the experimental animals showed a marked gain over the controls. Working with twice as many animals, I found the two groups as close together as could be expected, when a small number of animals is used.

So much importance is attached to the difference between Downs and Eddy's "secretin" and control groups that a careful analysis of the data seems necessary.

In comparing the percentages of gain in red blood cells it should be noted that the absolute difference between the two groups at the end of the experiment was only 203,000. The gain when expressed in percentage of the initial count seems to indicate a greater difference (secretin, 134.9 per cent—control, 116.43 per cent). This greater difference in the percentage of the initial count is due more to the lower count in the "secretin" group at the start of the experiment than to the relatively slight difference at the end. This may be illustrated by considering what the result would be in the case of rabbit 1 alone. The final count in this case would be 114.4 per cent of the initial count. This is less than the control gain. Therefore, the whole difference between the two groups rests on the fact that rabbit 2 had a temporary low count at the beginning of the experiment.

Any animal started at a count between 4,000,000 and 5,000,000 must show a gain when expressed in percentage of the initial count, as that is the low point in the animal's normal cycle. Nor is there anything unusual in such a count, as is evidenced by the fact that five of the eight animals used by me had counts between 4,000,000 and 5,000,000 some time during the eight weeks. As a matter of fact, it is obvious from both sets of data that, in general, any rabbit's count runs more or less in cycles varying from somewhat over 4,000,000 to somewhat over 7,000,000. For this reason any percentage of gain based on an initial count is so difficult of interpretation as to render its value doubtful.

A much better way of interpreting such data is to average the nine counts given for each animal. When this is done, one arrives at the following result (table 5):

"Secretin" Rabbits.	
Rabbit 1.—Average of all counts	6,248,000
Rabbit 2.—Average of all counts	5,928,000
Average for the group	6,088,000
Control Rabbits.	
Rabbit 3.—Average of all counts	6,208,300
Rabbit 4.—Average of all counts	6,576,800
Average for the group	6,392,550

This tabulation shows that the control group had a higher average than the "secretin" group, the difference being 304,550.

Similar data on my eight weeks' experiment are as follows (table 6):

"Secretin" Rabbits.	
Rabbit 29.—Average of all counts	6,042,500
Rabbit 33.—Average of all counts	6,098,300
Rabbit 34.—Average of all counts	5,247,000
Rabbit 44.—Average of all counts	5,034,300
Average for the group	5,605,525
Control Rabbits.	
Rabbit 23.—Average of all counts	5,548,800
Rabbit 28.—Average of all counts	6,128,400
Rabbit 38.—Average of all counts	7,119,200
Rabbit 40.—Average of all counts	4,935,800
Average for the group	5,933,050

The control group had a higher average, the difference being 327,525. This compares well with the difference between the two groups of Downs and Eddy (304,550).

Both sets of data show that the difference between the experimental and control groups is in favor of the control group.

The reticuloycte count varied from week to week, but when an average of the whole period is taken, the values for experimental and control groups correspond well, being 3.44 and 3.06 per cent, respectively. The experimental group shows the higher value, as would be expected from its slightly lower count.

COMMENT

The object of this paper is not to present a complete consideration of either regeneration or secretin, but to call attention to some well established facts concerning both, with which the conclusion that secretin is a stimulant of blood-forming tissue cannot be reconciled.

The facts on which the conclusion was based have been reviewed. In the first place, the sudden rise in red count observed (after the injection of the tissue extract), which returned promptly to normal, should not have been interpreted as suggestive of a regenerative phenomenon. The literature is replete with warnings on the point. Secondly, the data obtained in the long experiment (eight weeks), when interpreted in the light of knowledge concerning the normal cyclic fluctuation in the rabbit, do not furnish any evidence to support the contention that the experimental group showed more gain than the controls.

It would scarcely be logical to suppose that the small amount of secretin injected could produce so marked an effect, considering the relatively large amounts normally liberated, and it has been pointed out that the hormone is effective only when given intravenously.

It was likewise pointed out that substances present in the tissue extract used have been known for some time to cause transient concentrations of the blood.

Before concluding that a rise in red cell count is due to regeneration, it is necessary to show that the well known histologic signs of regeneration are present.

CONCLUSION

The rapid and transient rises in cell count reported to follow the subcutaneous injection of the tissue extract containing secretin are corroborated. The rises are not due to regeneration, but to a concentration of the blood which is a characteristic response to such extracts.

A NEW CLINICAL TEST FOR TISSUE THIRST*

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Recent reports by Aldrich,[1] who made tests by intradermal injections of physiologic solution of sodium chloride, showed clearly that edema was due to an increased hydrophilic action of the tissue colloids and not simply to renal obstruction. With this point in view, the following method was devised to study the colloid affinities of the proteins in the blood.

EXPERIMENTAL WORK

The apparatus used was a glass tube with a bell-shaped end. The bell end was closed with a collodion membrane, and the tube was filled with serum with a fine bacteriologic pipet. The tube was so graduated that when filled to a certain point it would read in percentage of swelling of the original volume of serum, as is shown in the illustration.

The ends of these tubes were then immersed in hundredth-normal hydrochloric acid, and the percentage of swelling was noted.

Dialysis of the same serum against water, physiologic solution of sodium chloride and various strengths of hydrochloric acid soon showed us that hundredth-normal hydrochloric acid gave the greatest amount of swelling. It is also true that variations in the thickness of the membrane within rather a wide range did not give variations in the amount of the swelling.

A series of serums from normal dogs and from normal persons were tested, and the amount of swelling was slight (table 1). Most of them swell 1 or 2 per cent, and 8 or 9 per cent is the maximum. In this connection it is interesting to note that in the appended list of controls numbers 17 and 18 showed considerable swelling, and subsequent study of the patients revealed that renal disease was present.

In a large series of cases this dialysis test was applied to nephritic and edematous patients. There was invariably a marked swelling. This ranged from 15 to 50 per cent (the limit of reading). Table 2 shows that this increased hydrophilic power of the serums is present not only in nephritis and uremia but also in edema of cardiac origin. In two cases of obstructive anuria there was little swelling (table 2).

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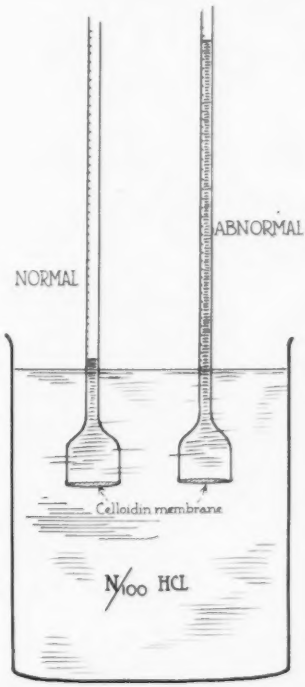
* From the Department of Surgery, University of Illinois College of Medicine.

1. Aldrich, C. A., and McClure, W. B.: The Intradermal Salt Test, J. A. M. A. **82**:1425 (May 3) 1924. Aldrich, C. A.: The Clinical Course of Generalized Edema, J. A. M. A. **84**:481 (Feb. 14) 1925.

COMMENT

The essential differences between uremic serums and normal serums consist in (1) greater acidity, (2) an increased amount of chlorides and (3) an increase in the amount of nonprotein nitrogen.

With these points in view, the normal serums in both dogs and human beings were (1) acidulated by various means, (2) the sodium chloride content doubled and (3) large amounts of urea added. None of



The tubes are first sealed at the bell-shaped end with a collodion membrane. They are then filled with serum up to the zero mark with a fine pipet and are finally immersed in hundredth-normal hydrochloric acid.

these procedures increased the hydrophilic power of normal serums to the slightest extent.

It is safe to assume, therefore, that this phenomenon resides in the character of the proteins in the serum. It is all the more striking when one considers that the uremic serums usually contain materially less protein than normal serums; and that in spite of this fact the protein which they do contain is able to absorb more water (table 3).

TABLE 1.—*Controls*

Diagnosis	Per Cent Increase	Remarks
1. Normal	7	
2. Pneumonia	2	
3. Normal	6	
4. Normal	9	
5. Old fracture	3	
6. Normal	1	
7. Old fracture	1.5	
8. Old fracture	6	
9. Herniotomy, eight days	0	Local anesthesia
10. Carcinoma colon	3	
11. Fibroma	1.5	
12. Normal	3	
13. Old fracture	0.5	
14. Normal	4.0	
15. Appendectomy, four days after operation.	8.0	
16. Normal	4.0	
17. Amputation, two months	10.0	Albuminuria, noted subsequently
18. Normal	16.5	Albumin and casts noted subsequently

TABLE 2.—*Nephritis*

Diagnosis	Per Cent Increase
1. Edema, cardiac	18
2. Chronic nephritis	12
3. Dysentery and dehydration	14
4. Cardiac edema	8
5. Nephritis with edema	14
6. Nephritis with edema	10
7. Diabetic acidosis	11
8. Decompensation, edema	14
9. Same case compensated	7
10. Postoperative vomiting	17
11. Severe hemorrhagic nephritis	28
12. Parenchymatous nephritis	36
13. Uremic coma	50+
14. Uremic coma	50+
15. Malignant hypertension	50+
16. Acute nephritis, child	48
17. Two day anuria	50+
18. Beginning uremia twitching	40
19. Polycystic kidney anuria	50
20. Uremic hiccoughs	28
21. Prostatic obstruction anuria	1.6
22. Prostatic obstruction anuria	2.4

TABLE 3.—*Relation of Protein Content to Swelling*

	Per Cent Swelling	Refractometer Reading
Normal human being (6 cases)	+ 5.4	56.2
Human being with mild uremic condition	+22	50.4
Human being with severe uremic condition	+34	48.6
Human being with terminal uremia	+39	43.4
Child, anuric for eleven days	+61	40.0
Human being with cardiac edema	+18	49.8
Human being with renal edema	+33	48.4
Acute nephritis, increasing edema	+41	46.2

TABLE 4.—*Relation of Protein Content to Swelling*

Source of Serum	Per Cent Swelling	Refractometer Reading
Dog 1, before injection	+ 7	56.4
Dog 1, after injection (uremic)	+51	43.6
Dog 2, before injection	+ 4	53.7
Dog 2, after injection (uremic)	+33	42.0
Dog 3, before injection	+ 9	54.2
Dog 3, after injection (uremic)	+41	40.4

More striking still is the set of experiments on artificial uremia in dogs as previously reported by one [2] of us (table 4). In each of the three experiments, the protein content of the serum as measured by the refractometric reading fell about 25 per cent, but in spite of this fact it was able to absorb a great deal more water. Only two interpretations of these results are possible. In the serums exhibiting abnormal swelling, there is either (1) a foreign substance as protein, which enormously increases the osmotic pressure or is combined with a serum protein to do so, (2) or else the serum protein has undergone a profound change, perhaps a greater colloid dispersion, increasing its osmotic pressure abnormally. All present thought in nephritis points in this direction.

CONCLUSIONS

1. A simple method of measuring the degree of swelling of serum protein when dialyzed against hundredth-normal hydrochloric acid is described.

2. The swelling of normal serum is slight, that from nephritic and edematous cases very great.

3. This phenomenon is due either to the presence in the blood of some foreign protein or to some change in the colloid dispersion of normal blood proteins.

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2. Andrews E.: Experimental Uremia, Arch. Int. Med. **40**:548 (Oct.) 1927.

DOES COMMERCIAL INSULIN CONTAIN WHAT HAS HITHERTO BEEN CALLED VITAMIN B?*

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Studies on the occurrence of what has hitherto been called vitamin B have shown that this food factor is widely distributed in nature. It is found in most common foods of both plant and animal origin (Osborne and Mendel,[1] Sherman and Smith,[2] McCollum and Simmonds[3] and Sherman[4]). Its distribution in animal tissues was investigated by Cooper,[5] who used the pigeon method and found that the liver and cardiac muscle of the ox were good sources of the antineuritic, water-soluble vitamin. Similarly, Osborne and Mendel,[6] using the growth of rats as the criterion for the presence of the water-soluble B-vitamin, reported that such tissues as the heart, liver, brain and kidney of the pig were rich in this food factor.

The presence of vitamin B in hormone preparations, however, is not so well known. A review of the literature revealed a paucity of such observations. Eddy[7] demonstrated the presence of vitamin B in an extract made from the pancreases of sheep. From the results of feeding experiments with white rats, this investigator concluded that "the water-soluble portion of the alcoholic extract of pancreas contains a substance that is capable of inducing marked increase in growth." Likewise, Swoboda,[8] using the yeast multiplication method, found that vitamin B was present in the pancreas and other glandular tissues.

During the course of an investigation concerning the physiology of vitamin B in the dog, it proved desirable to know whether commercial

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* From the Laboratory of Physiological Chemistry, Yale University.

* The experimental data in this paper are taken from the dissertation submitted by Charles J. Stucky in partial fulfilment of the requirement for the degree of Doctor of Philosophy, Yale University, 1927.

1. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **32**:309, 1917.

2. Sherman, H. C., and Smith, S. L.: The Vitamins, New York Chem. Catalog Co., 1922.

3. McCollum, E. V., and Simmonds, N.: The Newer Knowledge of Nutrition, ed. 3, New York, The Macmillan Company, 1925.

4. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 3, New York, The Macmillan Company, 1926.

5. Cooper, E. A.: J. Hyg. **12**:436, 1912; J. Hyg. **14**:12, 1914.

6. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **32**:309, 1917; **34**:17 1918.

7. Eddy, W. H.: J. Biol. Chem. **27**:113, 1916.

8. Swoboda, F. K.: J. Biol. Chem. **44**:531, 1920.

insulin contained appreciable quantities of this food factor. A comparison of the general properties of insulin (Macleod [9]) with those of vitamin B (Sherman [4]) makes it not at all unlikely that this accessory food substance is present in the hormone preparation. Study of the literature did not reveal that tests of this hormone for its vitamin B content had ever been made. Experiments with young rats were therefore performed. The curative type of procedure (in this case ability to restore growth) was employed, because it did not require the use of such large quantities of the insulin preparation.

EXPERIMENTAL DETAILS

The tests for vitamin B were made on a group of ten albino rats [10] of the same litter, the individual animals weighing between 30 and 40 Gm. at 21 days of age. They were placed in cylindrical, wire mesh cages with raised screen floors to prevent access to excreta (Steenbock, Sell and Nelson [11]). Each rat was caged separately and handled according to the technic developed in this laboratory (Smith, Cowgill and Croll [12]).

Vitamin B Deficient Ration

	Per Cent
Meat residue *	18
Corn starch	50
"Crisco"	23
Cod liver oil	5
Salt mixture †	4

* This substance is practically free from vitamin B (Cowgill, G. R.: Am. J. Physiol. **79**:341, 1926.) It may be obtained from the Valentine Meat Juice Company, Richmond, Va.

† The salt mixture described by Osborne and Mendel (J. Biol. Chem. **32**:374, 1917) was employed.

The insulin used in this investigation was of standard purity. In preparing the hormone for the feeding experiments, 4,500 units of the aqueous solution (insulin, Lilly [13]) were mixed with 4.5 Gm. of pure dextrin. This mixture was placed in an evaporating dish and heated gently over a hot plate for about four hours with occasional stirring, the temperature of the mixture being kept below 75 C., to avoid any possible destruction of vitamin B. At this temperature and for a considerable range above it, the vitamin has been shown to be stable (Sherman [4]). When thoroughly dry, the mixture was pulverized. The resultant product, a yellow-brown, sandy powder, was used for the vitamin B tests. Approximately 100 mg. of this insulin-dextrin preparation was equivalent to 100 units of insulin.

9. Macleod, J. J. R.: Physiol. Rev. **4**:21, 1924.
10. Obtained from the Albino Supply, Inc., Philadelphia.
11. Steenbock, H.; Sell, M. T., and Nelson, E. M.: J. Biol. Chem. **55**:399, 1923.
12. Smith, A. H.; Cowgill, G. R., and Croll, H. M.: J. Biol. Chem. **66**:15, 1925.
13. Obtained from the Eli Lilly and Company, Indianapolis.

In the feeding trials, the rats were fed on a ration deficient in vitamin B, having the composition shown in the table. The animals were fed the basal diet and water ad libitum. Dried brewery yeast,[14] as a source of vitamin B, was fed apart from the ration at the rate of 100 mg. per rat a day. All of the rats were placed on this dietary régime for about ten days, after which rats 1, 2 and 3, the controls, were continued on this ration while the remaining seven animals were deprived of the yeast supplement. When failure in growth or decline in body weight occurred, each rat was given a daily dosage of 100 mg. of the insulin-dextrin preparation, fed separately from the rest of the ration, as a possible source of vitamin B. At the end of six days, the animals fed insulin had declined to such a great extent in body weight that 100 mg. of yeast was substituted for the insulin preparation; this resulted in an immediate resumption of growth in all of the rats so fed. The chart demonstrates this clearly and shows the ineffectiveness of the insulin-dextrin preparation as a source of vitamin B.

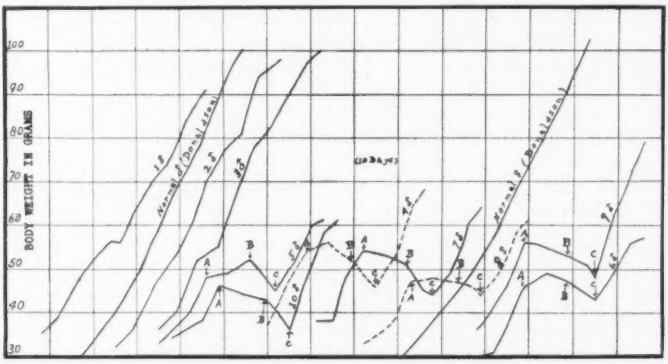

Chart showing that a young rat fed on a vitamin B deficient diet continued to decline in growth when receiving a daily supplement of 100 mg. of an insulin-dextrin preparation as a possible source of vitamin B. The substitution of yeast for the insulin preparation was followed by an immediate resumption in growth. Each of the control animals (1, 2 and 3) received the same ration plus 100 mg. of yeast daily from the beginning of the experiment. *A* represents the yeast withdrawn; *B*, the insulin added; *C*, the insulin replaced by yeast.

COMMENT

From the results of the experiments it is obvious that the insulin-dextrin preparation here used is markedly deficient in part, at least, of the complex hitherto known as vitamin B.

Recently, papers have appeared bearing on the possible plural character of vitamin B, so called.[15] Although the experiments reported here were performed on rats, it is worth noting that a few attempts to cure

14. Obtained from the Northwestern Yeast Company, Chicago.

15. Sherman, H. C., and Axtmayer, J. H.: A Quantitative Study of the Multiple Nature of Vitamin B, J. Biol. Chem. **75**:227 (Oct.) 1927.

polyneuritic pigeons by large doses (from 50 to 100 units) of insulin per os were made in this laboratory [16] and negative results were obtained. In these experiments the hormone was administered without further treatment, i.e., it was not evaporated down to dryness on dextrin as in the experiments on rats. It would seem, therefore, that insulin is at least deficient in the antineuritic substance.

SUMMARY

A commercial insulin preparation was tested for its vitamin B content on a group of young albino rats. From the results of the feeding trials, it may be concluded that such material, when added to a diet deficient in vitamin B, will not support growth. Tests made with pigeons suggest that the antineuritic factor also is absent. Whether the heat-stable growth promoting factor, in what has hitherto been spoken of as vitamin B, is absent was not determined.

16. Experiments performed by Miss Margaret H. Jones, B. A., of the Graduate School, Yale University.

SKIN SENSITIVITY OF RHEUMATIC SUBJECTS TO STREPTOCOCCUS FILTRATES

ITS RELATIONSHIP TO RHEUMATIC FEVER *

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The following work was carried out in order to determine whether one strain or a group of strains of streptococci exist which could be classed as rheumatic on the basis of the skin reactions in rheumatic subjects, and further to find if any immunologic characters were common to the varied types of streptococci which may be isolated in cases of rheumatic fever and chorea.

Attempts made to isolate streptococci from the blood stream were largely unsuccessful. Thirty-three blood cultures were made from twenty-nine subjects, and the technic advocated by Clawson [1] was employed. All of the subjects were acutely sick with rheumatic manifestations, and the fever at the time of culture varied between 38.6 and 40 C. (101.5 to 104 F.). All except four had cardiac involvement. Eleven had pericarditis and ten had subcutaneous nodules. The cultures were kept from four to six weeks and examined semiweekly. Contamination with air organisms occurred in a few instances, otherwise all the blood cultures were sterile with one exception, a culture of the heart blood obtained immediately post mortem. A small gram-positive diplostreptococcus of the gamma type was obtained on this occasion, but did not grow on subsequent transplants. Cultures of spinal fluid in chorea and of joint fluid in acute articular rheumatism have been negative in every instance, although a small gram-positive diplostreptococcus was isolated on one occasion from a rheumatic pericardial effusion. It, too, did not grow on subsequent culture and its reaction on blood medium is unknown.

The "rheumatic" strains of streptococci finally employed were all obtained from the upper respiratory tract of children with rheumatic manifestations. Since streptococci may be obtained from a large proportion of cultures from the nasopharynx, and from the throat and tonsils, cultures were not considered suitable when the number of streptococci was very small. Thus, of seventy-six cultures made, fifty-six strains of streptococci were considered sufficiently predominant to be suitable. Rather more than one half of the strains were isolated

* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Clawson, B. J.: J. Infec. Dis. **36**:444, 1925.

from the interior of the excised tonsils of convalescent rheumatic children. The remainder were obtained chiefly from the throats of subjects with acute rheumatic manifestations. A few were from sinus washings and ears where such foci seemed etiologic. In our series of cases, green streptococci could be isolated with equal ease during the acute and convalescent stage of the disease. Hemolytic strains were not commonly isolated during the period of acute sore throat, but were usually obtained during convalescence.

CLASSIFICATION OF ORGANISMS

The streptococci fell into two main classes: hemolytic and anhemolytic. The majority in the latter class were green, but five gray strains resembling, at least morphologically, the organism described by Small were included. The organisms were further classified according to their sugar fermentations. The sugars used were lactose, saccharose, inulin, salicin, mannite and raffinose. It was found that fourteen strains fermented lactose, saccharose and salicin and did not ferment mannite and raffinose. Three of these strains were green, the rest were hemolytic. The remaining strains showed considerable variation in their fermentation reactions. According to Andrewes' and Horder's [2] classification, most strains fell into the *salivarius* group, although three were classed as *fecalis* by their fermentation of mannite and a further two as *Streptococcus pyogenes*. This heterogeneity has been rather a general observation in previous studies of the organisms in the mouth in rheumatic fever.[3] None resembled Small's [4] strains in fermenting inulin. Similar fermentation tests made on a few of the control strains of streptococci, which will be described later, showed a predominating fermentation of lactose, salicin and saccharose, while one strain also fermented mannite. Thus the fermentation reactions did not distinguish the rheumatic strains from those of the control series. The organisms were also distinguished as scarlatinal and nonscarlatinal, both according to the skin reaction of the filtrate in groups of subjects with a positive reaction to the Dick test and those with a negative reaction, and by the ease with which intradermal injections of filtrates of streptococci belonging to the scarlatinal group were neutralized by either convalescent scarlet fever serum or commercial antitoxin when suitably diluted. None of the strains from rheumatic subjects fell typically into the class of scarlatinal strains. In nineteen filtrates from rheumatic sources, neutralization with scarlet fever serum occurred in five instances and

2. Andrewes, C. H., and Horder, T.: Lancet **2**:775, 1906.

3. Andrewes, C. H.; Derick, C. L., and Swift, H. F.: J. Exper. Med. **43**:13, 1926.

4. Small, J. C.: Am. J. M. Sc. **173**:101, 1927.

was partial in four of these. The same filtrates, however, were rather easily neutralized by the serum of subjects giving negative reactions to this filtrate. Three of the control strains were neutralized completely by scarlet fever serum and showed intradermal reactions consistent with the Dick reaction of the subject.

These figures are lower than those of Williams,[5] who obtained neutralization with scarlet fever antitoxin in 42.8 per cent of her filtrates of streptococci from excised tonsils.

The control group of streptococci consisted of twenty-four strains, ten hemolytic and twelve anhemolytic, isolated from the tonsils, throats and maxillary sinuses of nonrheumatic children.

EXPERIMENTAL METHOD

Technic of Growth.—The material was seeded on blood agar plates, immediately after it was obtained. Aerobic and anaerobic cultures were examined after twenty-four hours, and when streptococci were present in abundance, flasks of veal infusion broth with 0.1 per cent dextrose and a p_H of 7.8 were inoculated and incubated for four days. It was found that usually anaerobic cultures were more abundant than aerobic, but none of the strains were strict anaerobes. The cultures were then centrifugalized, filtered through a Mandler filter and incubated over night as a test of sterility.

Dilution of Toxin.—The concentrated filtrate was diluted with normal salt solution until a 1:500 dilution was reached. At first dilutions of 1:100 and 1:250 were used, but it was felt that the uniform use of a rather high dilution would rule out those atypical reactions which occur with low dilutions in some persons, and which are due to sensitivity to some constituent of the filtrate other than the toxic principle. The amount injected was 0.1 cc., and the site used was the anterior aspect of the arm or forearm. The reactions were controlled by intradermal injections of filtrate, 1:500, heated for two hours at 100 C. and of sterile medium similarly diluted.

Subjects Used.—Two main groups of children were employed: a rheumatic group and a control group. The former consisted of seventy-five children between the ages of 5 and 15 years who were or had been suffering from chorea, rheumatic fever or rheumatic carditis. All were patients in the St. Louis Children's Hospital or the country department at Ridge Farm. They represented varying degrees of severity and were in different stages of sickness at the time examined. Many had been under continuous observation for over a year, and changes in their reaction to the various filtrates were noted and correlated with their physical condition. The control group consisted of 200 children of the same age group and from the same institution or from the Shriner's Hospital for Crippled Children. They did not have any history or physical signs of rheumatic stigmas. This control group was divisible according to the Dick reaction, 100 being positive to 2 standard skin test doses (STD) of Dick toxin and 100 negative to 50 STD of Dick toxin. This division was thought advisable, as it was considered that sensitivity of subjects to the Dick tests might run parallel to their sensitivity to other streptococcus filtrates. Hence, rheumatic subjects should not only be controlled by nonrheumatic subjects, but they should be compared with controls reacting similarly to the Dick test. The reactions were read at the end of twenty-four hours. Posi-

5. Williams, A.: Am. J. Pub. Health **15**:129, 1925.

tive reactions measured 10 mm. or more in diameter and usually resembled the Dick test. Frequently, the heated control showed a reaction as large as that produced by the unheated filtrate. This seemed to occur more frequently in some persons than in others, and in such instances neutralization tests with serum were not satisfactory.

RESULTS OF INTRADERMAL INJECTION OF FILTRATES FROM RHEUMATIC STRAINS

Forty-three filtrates, twenty-two from hemolytic and twenty-one from anhemolytic streptococci were tested on two main groups of rheumatic and nonrheumatic children. Each toxin was tested on at least thirty persons, ten of the rheumatic and twenty of the control series, the latter group being again divisible according to the Dick reaction. Ten of the filtrates as judged by this method were apparently nontoxic; this conclusion was reached only after at least thirty children had been

TABLE 1.—*Results of Intradermal Injection of Streptococcic Filtrates from Rheumatic Sources*

	No. of Intradermal Injections on Rheumatic Group	No. of Positive Reactions on Rheumatic Subjects	Percentage of Positive Reactions on Rheumatic Subjects	No. of Intradermal Injections on Control Group	No. of Positive Reactions on Control Subjects	Percentage of Positive Reactions on Rheumatic Subjects
Hemolytic and anhemolytic strains	487	111	22.8	829	106	12.70
Hemolytic strains only	311	96	30.86	481	98	20.36
Anhemolytic strains only	176	15	8.50	348	8	2.30

tested and had given negative reactions. Most of these nontoxic filtrates were obtained from anhemolytic strains, only one hemolytic organism failing to produce toxin.

The total number of intradermal injections made into all subjects with filtrates from rheumatic subjects was 1,316, of which 217 resulted in positive reactions. Thus, the percentage of positive reactions in the entire group of children under observation was 16.5. An analysis of the intradermal injections is given in table 1 to show the marked difference in the response of the rheumatic subject as compared with that of the control. It will be seen that the percentage of rheumatic children reacting positively is almost double that of the control series. This disparity is especially striking when the anhemolytic filtrates are studied separately, when the rheumatic subjects are shown to be about four times as susceptible as the controls. Birkhaug [6] and Kaiser,[7] using a similar technic and a filtrate from a "rheumatic" strain of streptococcus, demonstrated the increased skin sensitivity of rheumatic subjects.

6. Birkhaug, K.: J. Infect. Dis. **40**:549, 1927.
7. Kaiser, A. D.: J. Infect. Dis. **42**:25, 1928.

On the other hand, when one studies the sensitivity of this entire group of children to filtrates of streptococci obtained from nonrheumatic subjects, one is struck with the resemblances between the results in the two series. A total of 553 intradermal injections made in this group showed 16.66 per cent positive reactions—close to the 16.5 per cent of positive reactions obtained with the "rheumatic" filtrates. The resemblances hold when a more detailed study is made, as is outlined in table 2.

Here it will be seen that the percentages lie close to those given in table 1, and again that although a fairly wide difference exists in the sensitivity of the two groups to the hemolytic strains, this difference is greatly exaggerated when the anhemolytic group is studied. It is realized that the total number of positive reactions to the green and gray varieties of streptococci is small, but the difficulty of producing a

TABLE 2.—*Results of Intradermal Injection of Streptococcic Filtrates from Sources Other than Rheumatic*

	No. of Intradermal Injections on Rheumatic Group	No. of Positive Reactions on Rheumatic Subjects	Percentage of Positive Reactions on Rheumatic Subjects	No. of Intradermal Injections on Control Group	No. of Positive Reactions on Control Subjects	Percentage of Positive Reactions on Rheumatic Subjects
Hemolytic and anhemolytic strains	204	50	24.5	348	42	12.0
Hemolytic strains only	121	36	29.7	156	34	21.8
Anhemolytic strains only	83	14	16.8	192	8	4.2

toxic filtrate from anhemolytic strains of streptococci is well known. With other methods of culture and with the injection of lower dilutions of filtrate, more striking figures might be obtained, but on the other hand, the differences between the sensitivity of the rheumatic and control groups are sufficiently striking and it was felt advisable to keep the results as closely analogous as possible to those obtained with hemolytic strains. It was of interest to note that children belonging either to the rheumatic or to the control group who responded with positive reactions to one filtrate were likely to respond positively to several. The same held true for children with negative reactions. As it has been shown that many streptococci and also pneumococci have a nucleoprotein antigen in common to several strains,[8] it seems possible that filtrates from such organisms may possess antigen characteristics in common and thus explain the tendency by which persons react to more than one filtrate.[9]

8. Avery, O. T., and Heidelberger, M.: J. Exper. Med. **42**:367, 1925. Lancefield, R. C.: Proc. Soc. Exper. Biol. & Med. **22**:109, 1924-1925.

9. Zinsser, H., and Tamaya, T.: J. Exper. Med. **42**:311, 1925.

COMPARISON BETWEEN THE DICK TEST AND SENSITIVITY TO THE FILTRATES STUDIED

As was already explained, it was felt that the sensitivity of subjects to streptococcus filtrates might be to some extent parallel to their Dick reaction. If this were so, an error might be introduced, owing to the selection of two groups of unequal size in which the number of subjects in each group who gave positive reactions to the Dick test probably differed. The figures were, therefore, restudied from this new standpoint. By this comparison, an interesting difference was brought out in the sensitivity of rheumatic and control subjects. Consideration, first, of the filtrates from rheumatic sources shows (table 3) that the rheumatic subjects who gave a negative reaction to the Dick test were

TABLE 3.—*Comparison Between Sensitivity to the Dick Toxin and to Streptococcic Filtrates from Rheumatic Sources*

	Rheumatic Subjects			Control Subjects		
	Total Intradermal Injections	+	Per Cent Positive	Total Intradermal Injections	+	Per Cent Positive
Dick positive...	148	25	16.9	293	68	17.1
Dick negative..	318	78	24.5	437	39	8.9

TABLE 4.—*Comparison Between Sensitivity to the Dick Toxin and to Streptococcic Filtrates from Sources Other than Rheumatic*

	Rheumatic Subjects			Control Subjects		
	Total Intradermal Injections	+	Per Cent Positive	Total Intradermal Injections	+	Per Cent Positive
Dick positive...	72	18	25.0	172	26	15.1
Dick negative..	138	32	23.1	176	16	9.9

apparently considerably more susceptible to the filtrates than those in the group with the positive reaction. The control subjects, however, showed what one would have expected, namely, a greater percentage of positive reactions among the subjects positive to the Dick test. On the other hand, similar study of the control filtrates shows results which are much closer to those which were expected. The rheumatic subjects who are positive to the Dick test are slightly more sensitive than those who are negative. Of the control subjects, the relative sensitivity of the subjects positive to the Dick test and those negative to it is almost identical with that shown in table 3.

IS SENSITIVITY DEPENDENT ON THE TYPE OF RHEUMATIC MANIFESTATION OR ON THE STAGE OF THE DISEASE?

It was felt that if a positive reaction occurring in a rheumatic child was evidence of a rather specific sensitization, this sensitivity might vary

with the type of rheumatic manifestation present and also with the course of the disease. By watching a group of such children for some time, the reaction which took place to intradermal injections could be compared with the clinical observations. The results of this observation are shown in table 5, which illustrates two interesting points: first, the low percentage of positive reactions obtained in cases of acute carditis often accompanied by low grade chorea or joint pains; second, the high percentage of positive reactions obtained in the series of cases of acute rheumatic fever and acute chorea in which the changes in the heart were slight or could not be detected clinically. More light was shed on this difference by following the results of some of the intradermal injections over a considerable period of time and correlating changes in reaction with clinical changes in the patient. The tests were repeated after periods of from one to eighteen months, and when changes were observed, the intradermal injections were repeated many

TABLE 5.—*Percentages of Positive Reactions Occurring in Various Forms of Rheumatism and Stages of the Disease*

Type of Rheumatism Present at Time of Intradermal Injection	Rheumatic Filtrates Used		
	Total	Active	Clinically well or Inactive
Rheumatic fever	28.0	62.5 *	21.4
Chorea	25.6	34.6	22.5
Carditis, when acute frequently accompanied by chorea or rheumatic fever	20.5	10.5	21.97

*Series very small.

times. In thirty-one instances a changed reaction was observed. Three of these occurred in the control group of children and in those three cases acute infection or any other factor could not be traced as a reason for the change. Among the patients in the rheumatic group, the changes fall into two main types and may be summarized as follows: subjects with chorea or rheumatic fever in whom an overwhelming cardiac infection is not present passed from a stage of positive to negative skin reactions. This was almost invariably true in the cases that were followed and in which the reaction was positive during the acute stage, and was seen in fourteen instances. In only five children in whom the intradermal injections were repeated during the clinical course of the disease was no appreciable change of the skin reaction observed. This change may be analyzed further according to the appearance of the positive reaction. In some cases, the reaction resembled a Dick reaction. The controls of filtrates heated at 100 C. for two hours were negative, and the skin reaction was rather readily neutralized. In contrast with this were a large number of indurated reactions when the toxic substance was heat stable and when neutralization could not be effected. These

reactions lasted longer and resembled somewhat a Schick reaction. It was found that the commonest reaction obtained during the acute phase was the flat positive, and that during early convalescence practically every child showed an indurated positive response. The same intradermal injections repeated when the children were clinically well usually gave negative reactions, although in five instances the reactions did not become negative during the period of observation. In one instance, after going through the positive and negative phase, the test again gave a positive reaction. Three persons watched for over a year developed positive skin reactions when previously they had given negative reactions. In one case a mild acute rheumatism followed the change, while another child remained well. The third instance occurred in a child who had had chorea one year previously and in whom an effort had been made to produce skin sensitivity by injecting filtrate obtained from the subject's own throat organisms. The acquisition of skin sensitivity was followed by a recurrence of chorea, but it is felt that other factors played a more important rôle. This phasic change of the skin reaction during rheumatic manifestations has an interesting parallel in the work of Dochez and Stevens [10] on experimentally produced allergy.

An apparently different type of changed reactivity from that just described was seen in those patients who after showing a positive reaction developed a fulminating carditis with high temperature, pericarditis and pulmonary involvement. In five such instances, the positive test became negative, and in the only surviving patient a return to a positive reaction was observed as recovery occurred. The same phenomenon was observed a second time in the same patient during a subsequent recrudescence of rheumatic pleuritis. This altered reactivity may be explained on the basis of anergy as a Dick test was similarly diminished in those cases in which it had previously been positive. Anergy to tuberculin in rheumatic fever has been described in the literature.[11] Spontaneous loss of sensitivity to streptococcus filtrate occasionally occurs without obvious infection or operative procedure to explain the change.

NEUTRALIZATION OF INTRADERMAL INJECTIONS WITH SERUM OF SUBJECTS FROM WHOM STRAIN WAS OBTAINED

Samples of serum were obtained from most of the subjects during both the acute and the convalescent stage of the disease. This serum was mixed with the diluted filtrate of the organisms from the same subjects from whom the serum was obtained and injected intradermally

10. Dochez, A. R., and Stevens, F. A.: J. Exper. Med. **46**:487, 1927.

11. Magni, Luciano: Riv. di Clin. Pediat. **25**:27, 1927; abstr., Am. J. Dis. Child. **33**:991 (June) 1927.

into persons with positive reactions. The filtrate was diluted so that 0.1 cc. contained 4 STD. It was then mixed with double the volume of serum and incubated for one hour. It was thought that a difference in the neutralizing properties of the serum taken at different stages of the disease might be demonstrable. It was found, however, that neutralization was easily effected in the majority of cases and no difference could be demonstrated in the neutralizing power of acute or convalescent serum of the same subject. In four instances, neutralization did not occur, although the subjects from whom the organism and serum was obtained had negative skin reactions. Neutralization also occasionally occurred with the serum of subjects who gave positive reactions to intradermal injections of their own organisms. The serum of persons who gave negative reactions to the filtrates neutralized such filtrates rather readily on susceptible subjects. This observation is contrary to that of Mackenzie and Hanger,[12] but it is felt that as they injected much larger quantities of filtrate the reactions obtained were not entirely due to the neutralizible toxic substance.

ATTEMPT TO FIND CIRCULATING TOXIN IN THE BLOOD OF RHEUMATIC SUBJECTS

It was thought that if rheumatic fever depended, as scarlet fever apparently does, on the presence of a circulating toxic material, it would be possible to demonstrate this by injecting intradermally the serum of acutely sick children into rheumatic and nonrheumatic subjects. Twelve serums from acute cases with pericarditis, fever and rheumatic nodules were so tested on forty rheumatic and twenty control subjects. Positive intradermal responses measuring 10 mm. or more did not occur, although 0.3 cc. was injected each time. This does not rule out the presence of some toxic material in slight amounts, and it is possible that the serum was not taken from sufficiently early cases.

RESULTS OF INTRAMUSCULAR INJECTION OF TOXIC FILTRATE

A further attempt to trace a resemblance between the mechanism of rheumatic and scarlet fever was made by injecting increasing amounts (from 0.001 to 1 cc.) of toxic filtrate into subjects convalescing from chorea. One such patient in whom skin sensitization to the filtrate was already present developed fever, general malaise and local inflammation at the site of injection, but increase or decrease of her symptoms did not occur. A normal subject whose skin was sensitive showed exactly the same symptoms. Of the other two subjects who were given injections of filtrate from organisms from their own throats, one became

12. Mackenzie, G. M., and Hanger, F. M.: J. Immunol. **13**:50, 1927.

skin sensitive and subsequently developed chorea, and the other did not become sensitized or show any clinical change. It is felt that greater success might have been obtained if only subjects showing a positive skin test as evidence of the presence of an allergizing focus had been employed.

A difference was not noted in the toxicity of filtrates from streptococci isolated during the acute and convalescent stages of the disease, and a difference apparently did not exist in the toxicity of the organisms whether they were obtained from cases of rheumatic fever or chorea. Although the figures in table 1 give the impression that the filtrates of the various strains had a uniform distribution of positive reactions, this was not the case. Several filtrates, especially of hemolytic strains, gave identical percentages of positive reactions in the rheumatic and control series, and in a few the controls seemed relatively more susceptible. However, in a large proportion of the hemolytic and in most of the green strains, the increased susceptibility of the rheumatic subject was marked.

THE DICK TEST IN RHEUMATIC FEVER

The Dick test was studied in seventy-seven rheumatic subjects. All were given injections of 2, 20 and 50 STD of standard Dick material. It was found that seventeen, or 22 per cent, gave positive reactions and that sixty, or 78 per cent, gave negative reactions to 2 STD. These observations may be contrasted with those of Cooke [13] working with children of the same age group and in almost identical circumstances where 35.5 per cent were Dick positive. Zingher's [14] figures, although from a different group of children, accord with those of Cooke. Occasional spontaneous change of a positive to a negative reaction is seen in nonrheumatic subjects. This was seen once in a rheumatic child after an attack of acute tonsillitis which had many of the characteristics of true scarlet fever. This was the only instance in which a marked change occurred, the child being positive to 2 STD before the injection, and negative to 50 STD subsequently. In seven of twenty-eight cases in which the Dick test was made both during the acute and convalescent phase, a rather consistent change was seen. The test, negative during the acute phase, became positive. This temporary negativity of the Dick test in acute diseases has been the observation of others, and is an interesting contrast to the behavior of other streptococcus filtrates during the acute and convalescent stages of rheumatism.

13. Cooke, J. V.: Scarlet Fever: II. The Development of Toxin Sensitivity of the Skin in Infants and Its Relation to the Presence of Antitoxins in the Blood, Am. J. Dis. Child. **35**:762 (May) 1928.

14. Zingher, A.; quoted by Park, W. H.: Scarlet Fever: Etiology, Prevention by Immunization, and Antitoxic Treatment, J. A. M. A. **85**:180 (Oct. 17) 1925.

COMMENT

A survey of the literature for the last thirty years on the etiology of rheumatic fever shows a gradually increasing belief in its streptococcic origin. Most workers have felt that the specific characters of the disease must be due to a specific etiology, and many so-called rheumatic organisms have been described. The possibility of a specific reaction of certain persons to a heterogenous group of bacteria was suggested by Menzer [15] as early as 1902, but this lead has not been generally followed. The rare occurrence of streptococci in the blood and tissue fluids of rheumatic subjects and the inability to reproduce the disease by the most diverse methods of injecting streptococci leads one to believe that the disease is not produced by a blood stream infection. A heterogenous group of cocci may be etiologic, and in this connection Zinsser [16] mentioned an interesting case in which two distinct strains of streptococci, one a typical viridans and the other belonging to the gamma group, were isolated in a case of rheumatic fever. Swift and his colleagues [17] have also made this observation.

With the intradermal method of injection of the filtrable products of streptococcus, the rheumatic subject has been shown to be much more susceptible than the control to these filtrates as a group. This sensitivity, however, varies from the numerous positive reactions obtained when some filtrates are used to the slight sensitivity to others, including the Dick toxin. The validity of the skin test as a test of sensitivity may be questioned on theoretical grounds, but it is felt that sufficient analogy existed between rheumatism and tuberculosis to make the significance of the skin test possibly similar. The results obtained seem to have justified this assumption. It might be felt, too, that rheumatic subjects who are known to have frequent infections of the upper respiratory tract owe their skin sensitivity to these frequent infections and not to an underlying rheumatic condition. The evidence, however, suggests a closer relationship between positive reactions to intradermal injections and the rheumatic manifestations. Subjects who are suffering from acute diseases other than rheumatic conditions tend to give negative reactions during the acute stages of their illness and later, positive reactions; this has also been the experience of Mackenzie and Hanger.[12] A similar phenomenon occurs with the

15. Menzer, A.: Die Aetiologie des acuten Gelenkrheumatismus, Berlin, 1902; Ztschr. f. klin. Med. **47**:109, 1902.

16. Zinsser, H.: Bull. N. Y. Acad. Med. **11**:351, 1928.

17. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Bacterial Allergy to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, J. A. M. A. **90**:906 (March) 1928. Swift, H. F., and Kinsella, R.: Bacteriologic Studies in Rheumatic Fever, Arch. Int. Med. **19**:381 (June) 1917.

Dick reaction. Rheumatic children, on the other hand, show a positive intradermal reaction during the acute phase and tend to be negative during convalescence.

Dochez and Stevens [10] were able to watch the changing response to intradermal injections in rabbits immunized against an erysipelas strain of streptococcus. They found that an early negative phase was succeeded by a positive skin reaction and that this phase in turn could be subdivided into a primary stage in which the reaction was neutralizable and in which a reaction did not occur when the filtrate was boiled and into a second stage in which the reaction was not neutralizable and in which the filtrate if heated gave rise to reactions as extensive as those produced previously. The flat positive reaction followed by the indurated positive reaction in acute and subacute rheumatism and chorea are striking analogies to those reactions which were described by Dochez in the early stages of immunization. In his work and in the work presented in this paper, the positive response to intradermal injections was followed by a period of negativity. Only one of the patients was followed sufficiently closely to show a late return to the positive reaction, although three further instances occurred in which, after a period of negativity, the reaction again became positive. Although lacking completeness, these studies show the same trend as do those of Dochez in experimental allergy and thus link an allergy to streptococcus infections due to a wide variety of organisms with the picture of rheumatic fever. In the small group of cases in which an overwhelming cardiac infection occurred, the skin tests became negative. This was true for all the filtrate tests made on each subject and also for the Dick test. The Dick test also tended to be less positive during acute rheumatic conditions than it was after convalescence. In other words, the Dick test varied in rheumatic children as it does in other children during acute infections, while the behavior of streptococcus filtrates in fulminating carditis may be due to the same factors or may be explained by desensitization.

The low percentage of positive Dick tests occurring in this rheumatic group in which one would rather imagine it to run parallel with the high percentage of positive reactions with other filtrates was, at first sight, surprising. It was also difficult at first to conceive how one diverse group of streptococci could sensitize rheumatic children, while with other smaller equally diverse groups rheumatic subjects seemed as little or less susceptible than the controls. A possible explanation for both these differences may be found in the varying ability which different strains of streptococci possess in stimulating antitoxin production. Infection with the scarlet fever strain or strains usually results in the production of circulating antitoxin and of considerable immunity to the disease. This is not always demonstrable in other diseases of streptococcic origin in which the patient frequently remains susceptible.

It is thought that the low incidence of positive Dick reactions compared with the high incidence of positive reactions to intradermal injections of filtrates of other strains of streptococci may be correlated with the varying ability of different strains of streptococci to produce a neutralizing antitoxin. According to this theory, one would suppose that rheumatic subjects were hypersensitive to all streptococci from an early age, and that this increased sensitivity was masked in the case of scarlatinal and some other strains by the production of circulating antitoxin. Thus, the group of children with the low percentage of positive Dick tests would be that group most frequently infected by streptococci in general, and would show a high percentage of positive skin reactions to those other strains. On the other hand, among the controls in whom less infection with organisms of the upper respiratory tract had occurred, sensitivity to one organism, e.g., the scarlet fever streptococcus, would be paralleled with sensitivity to others, and the infection would have been insufficient to mask sensitivity by the production of antitoxin.

The technic of neutralization of products of streptococci with supposedly immune serum is less satisfactory than neutralization of the Dick toxin. In most of the persons who gave negative reactions to the filtrates, antitoxin could be demonstrated in the blood, but neutralization tests with such serums were not invariably successful; that is, in one or sometimes two of a group of four subjects on whom neutralization tests were made, neutralization could not be accomplished. Such tests were least successful when made on subjects in the subacute stage of rheumatic fever and chorea who showed an induration in the skin test with sensitivity to the heated filtrate. Difficulty was not experienced in neutralizing those tests in which the positive reaction occurred only with the unheated filtrate and the reaction was not indurated. The ability to neutralize such intradermal tests was first pointed out by Dochez and Sherman [18] and by Dochez and Stevens [19] working with erysipelas and scarlet fever strains of streptococci. No differences could be shown in the antitoxin titer of the serums taken from rheumatic subjects at different stages of the disease, and it is conjectured that the response of the rheumatic person does not involve to any extent the mechanism of antitoxin production.

The percentage of positive reactors among the control series of nonrheumatic children seems significant. Several of them showed the raised positive reaction similar to that occurring in rheumatic subjects. None, however, had a history or physical signs of rheumatic infection. It is probable that some difference exists in the tissues of rheumatic

18. Dochez, A. R., and Sherman, L.: Proc. Soc. Exper. Biol. & Med. **22**:282, 1925.

subjects which, with the acquired allergy to organisms common in the throat, determines the specific characters of rheumatic fever and chorea.

It would be rash to assert, on the basis of these observations, that in suitable persons all strains of streptococci could cause rheumatic fever and chorea. What seems probable is that rheumatic fever is an allergic response to common streptococci and occurs in certain persons whose tissues for some reason respond differently. It is possible to demonstrate this hypersensitiveness by using the products of all types of streptococci for intradermal injections. The possibility of rheumatic fever being caused by a certain special group of streptococci is not ruled out, for in this case the positive skin reactions to other strains could be explained by the nonspecific response of the tissues to an antigenic fraction common to a large group of streptococci. One feels, however, that this would be unlikely because of the heterogenous group of streptococci to be found in the tissues and throats of rheumatic subjects, and that at least the members of the wide anhemolytic group are most probably implicated.

SUMMARY

1. The streptococci of the upper respiratory tract of rheumatic children are identical culturally and immunologically with those from normal children.

2. Persons suffering from rheumatic fever show marked sensitivity of the skin to filtrates from a wide group of those streptococci either from rheumatic or normal subjects.

3. This sensitivity is most marked in the acute stages of rheumatic fever and chorea, especially when acute carditis is not present. It is least marked when the subjects are clinically well.

4. In those cases in which the skin reactions are followed over a period of time, it is possible to divide the skin reactions into definite phases which are analogous to certain cases of experimental allergy.

5. These observations indicate a definite relationship between rheumatic fever and streptococcal infections, but do not implicate any particular strain of organism. It is suggested that the rheumatic syndrome is an allergic response of certain predisposed persons to the common streptococci of the upper respiratory tract.

Book Reviews

CONSTITUTIONAL INADEQUACIES: AN INTRODUCTION TO THE STUDY OF ABNORMAL CONSTITUTIONS. By NICOLA PENDE, M.D., Professor of Clinical Medicine, Royal University of Genoa, Italy. Translated by Sante Naccarati, M.D., Sc.D., Ph.D., Associate Professor of Nervous and Mental Diseases, Post-Graduate Medical School of New York, New York City. With a foreword by George Draper, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Chief of Constitution Clinic, Presbyterian Hospital, New York City. Price, $3.50. Pp. 270, with index. Philadelphia: Lea & Febiger, 1928.

Shaw has taken us "back to Methuselah"; Pende takes us back to Hippocrates and Galen. This interesting monograph is a presentation, in the language of twentieth century biology and medicine, of the ancient idea of preponderance of specific humors or elements giving rise to the individual characteristics of a person. By constitution the author understands the hereditary potentialities of the individual protoplasm as modified by individual experience. "Constitution is determined principally by the internal evolutionary destiny assigned to each individual at the moment of conception."

We have no quarrel with this definition except the phrase: "at the moment of conception." Of course, it is clearly established that hereditary factors are present in the germ cells before the moment of conception. Nothing is given to the germ cells in the way of evolutionary potentials at the moment of conception except that which results from an admixture of the two germ cells. This conception of constitution is probably true, but is certainly not new.

According to Dr. Pende constitutional inadequacies are such defects or injuries, either originally hereditary potentialities or accidentally induced by environment, that prevent perfect internal coordination and perfect adjustment to the external environment. Such constitutional inadequacies constitute or lead to disease.

In the second chapter the author gives anthropometric measurements from which the attempt is made to predict the kind of constitutional inadequacies (diseases) that the person is apt to develop during the different stages of life. Like other authors of this school, Dr. Pende is strong on classification. He analyzes, criticizes, rejects or adopts elements of classification by previous authors who have written on constitutional pathology or disease as the expression of defects in the constitution. To what extent this type of work will advance medicine depends on the quantitative accuracy of the measurements or tests and on a number of persons included in the measurements. At present the whole matter is essentially an interesting working hypothesis. It has led to nothing definite in either therapy or prophylaxis.

Unfortunately, the volume is marred by a great many ambiguities. We are unable to state (not being familiar with the original Italian) whether these ambiguities are due to Dr. Pende or to the translator, Dr. Naccarati. Possibly some of the ambiguities are inherent in the theory, but occasionally they seem to be due merely to the love on the part of the author or the translator of sonorous sounds. For example "in the case of familial constitutional hypertonia that I have observed, the habitus of the patients corresponded to the megalosplanchnic hyperpituitary, hypergenital and hyperadrenal constitution. This accords well with the stimulatory action exerted upon the cardio-arterial muscular tonus by the genital, neurohypophysial and adrenal hormones, especially after puberty, and enables us to understand also how another constitutional anomaly coordinated with the preceding in these same individuals might be a vaso-motor nervous hyperexcitability, a tendency to angiospasm, a neuropathic diathesis, predominantly sympathicotonic since the aforesaid hormones stimulate the sympathetic tonus and excitability" (p. 156).

On pages 226 and 227 Dr. Pende comes dangerously near endorsing the superstition that individual experiences or so-called "impressions" on the part of the mother during pregnancy influence the fetus. He states: "Very important also are the changes that the fetal glands may undergo during intra-uterine life, as the result of toxic, toxinfectious or psychic influences acting upon the mother." "Now that we know the influence of the psychic upon the hormonic secretions and that of the hormones upon the great sympathetic system we can conceive how a nervous or psychic trauma of the mother might succeed in disturbing the endocrine balance of the fetus and hence its normal development."

The plain facts, of course, are that we do not know the influence of the psyche on the hormone secretion nor the influence of the hormones on the sympathetic system, and least of all do we know how such changes in the mother could possibly affect the fetus.

The final chapter is an appendix to the English translation with the heading "Modern Analysis of the Individual Human Biotype." The author here outlines (pp. 245 and 246) sixteen anthropologic, physiologic and psychic tests necessary to establish the particular individual's "biotype." Some of these tests such as anatomic measurements, body weight and basal metabolism are fairly quantitative, but the tests outlined under "neuro-vegetative orientation," "endocrine orientation," "tonus of the bodily form," "development of instinctive life," "development of moral life," "development of total intelligence," etc., are at present incapable of quantitative determination. One may talk about them and write about them without end, however.

Part of the obscurities of the volume are due to the frequent coinage of new terms. There is a four page glossary at the end of the book in which some of these terms are defined, but in some cases the definitions are as obscure as the terms. For instance, "cenesthesia — the subconscious sensation caused by the functioning of internal organs." What is a subconscious sensation? "Colloidoplasmatic — noting the relation of colloids and plasma." What notes what? Some of the new terms introduced seem superfluous and add to the difficulty of the reader. For instance "Hypo-evolutism" (hypoplasia); "impuberism" (infantilism); "tachytropism" (elevation of basal metabolism); "iso-ionia," etc.

The monograph is to be considered as a serious contribution to theoretical biology and theoretical medicine. It is challenging and interesting when the informed reader is able to follow the author and not flounder in the fog of obscurity, but many of the methods of investigation proposed will lead, not to light, but to still further verbalism and befuddlement.

THE BRAIN FROM APE TO MAN. A CONTRIBUTION TO THE STUDY OF THE EVOLUTION AND DEVELOPMENT OF THE HUMAN BRAIN. By FREDERICK TILNEY, PH.D., M.D. With Chapters on the Reconstruction of the Gray Matter in the Primate Brain Stem by Henry Alsop Riley and Foreword by Henry Fairfield Osborn. Price, $25. Two volumes. Pp. 1158, with 557 illustrations. New York: Paul B. Hoeber, 1928.

"The purpose of this work is to assemble and discuss the evidence of evolution contained in the brains of primates." This is the author's announcement of his program. The chief emphasis is laid on the brain stem and those parts of it that reflect changes in behavioristic adaptation to diverse modes of life. Special attention is paid to evidences of progress in the direction of human specialization during the transition from life in the treetops to life on the ground and in the open.

Is the book addressed to the lay public whose interest in problems of human evolution is still keen, or to the professional neurologists? After reading both of these ponderous volumes one is still in doubt. What one finds is apparently a technical subject matter in semipopular form. Some of us who have tried this enterprise ourselves know how difficult it is, and our own failures should make us charitable. The outcome in this case, however, is certainly not fortunate.

The accounts of the natural history and probable phylogeny of the primates from lemurs to men, and the analysis of the skeletal remains of our human and prehuman ancestors, with its wealth of pictorial illustration, seem to be intended for general readers, but they will not find it easy. Fondness for sonorous polysyllables gives evidence of great erudition, but one wonders how far the lay readers will go into description of this sort: "In hylobates the brachiating type of locomotion has replaced the pronograde specialization of lower primates."

Interlarded with these chapters are technical neurologic descriptions which are beyond the grasp of any but expert neurologists and which even for these are tantalizing because of their incompleteness and in some places their inaccuracy. The obvious things are pointed out with tedious reiteration, but the details of interest to neurologists are notably lacking. This leaves one with a feeling of exasperation, for when one expects exact description and illustration, one finds too often only banalities. The method of preparation of the measurements, indexes and reconstructions of internal organs of the brain stem are not given with sufficient precision to enable the critical reader to evaluate them, or in some cases to understand them. Illustrations are given of reconstructions of the gray matter of the brain stem of eleven species of primates, including man. When the pictures of reconstructions of the human brain stem are compared with the drawings of Weed's carefully made model, they seem to have little resemblance. Why is this? The photographs of the gross specimens leave much to be desired; and the accompanying key drawings, which we should expect to supplement the photographs, are too sketchy to add anything of value.

There is undoubtedly much of interest in these volumes, but as one puts them back on the shelf it is with a feeling of disappointment that so large a labor and so good a manufactured product, on the publisher's part, should be so blemished by inaccuracies and deficiencies as to fall far short of what a scientific treatise should be.

LOW BLOOD PRESSURE: ITS CAUSE AND SIGNIFICANCE. By J. F. HALLS DALLY. Price, $5. New York: William Wood & Company, 1928.

In recent years there has been a decided tendency toward interest in the subject of low blood pressure, perhaps because some of us are tired of the question of high blood pressure. The present book was written in the hope of presenting this subject from a broad biologic point of view. The general discussion of the physiologic significance of blood pressure is excellently given; then the author proceeds to the question of low arterial pressure, particularly in regard to its etiology. The standpoint is taken that patients with low arterial pressure may be considered as having a low vitality secondary to constitutional or to nutritional disorders or disturbances of the endocrine glands. It is assumed that a change occurs in the "acid-base tissue balance," so that these patients are much more likely to have a high ratio of alkali to acid in the urine. This biochemical change is given considerable emphasis without, however, a sufficient presentation of the actual facts underlying this supposed abnormality of metabolism. At any rate there is an excellent review of all the other views of the etiology of hypotension followed by a complete discussion of the multitude of conditions and diseases in which low blood pressure may be found.

The diagnosis and prognosis are intelligently discussed, and the chapter on the general management of low arterial pressure includes most of the measures which have been agreed on as beneficial for hyposthenic persons. In this chapter, however, one finds such suggestions as the subcutaneous injection of oxygen as a treatment. Organotherapy also is prescribed in a rather uncritical fashion, comprising extracts of thyroid, pituitary, suprarenal and gonadal glands either singly or combined. It is unfortunate that this last chapter contains a considerable amount of uncritical therapy.

On the whole, however, this book represents an excellent review with a thorough discussion of most of the significant literature on the subject of low blood pressure, and should be of value to all who are interested in this field of cardiovascular conditions.